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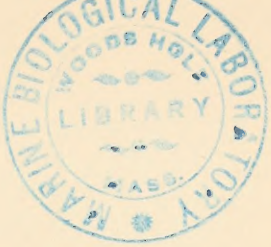

THE APPLICATION OF EXPERIMENT TO THE STUDY OF CANCER

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Dogmatic statements regarding the nature of cancer have broken more reputations than they have made. Paradoxical as it may be, progress in our knowledge of cancer has been made mainly by failure, by successive generations of investigators proving the insufficiency of the knowledge and the hypotheses of their predecessors; but this applies equally to the advancement of knowledge in many fields. The advancement of knowledge by the process of exclusion is surely the most tedious of methods, since, beyond all else, it signifies inability to formulate correctly the problem which it is sought to solve. We are still struggling to formulate correctly the problem, or better, problems of cancer, the sum of our facts not yet sufficing for an unequivocal statement of a problem which shall finally rid us of the everlasting question, What is the cause of cancer? We must be patient of the necessity for undertaking destructive work. In the face of the many defeats efforts at constructive work have suffered in the past, we must be mindful that hypotheses and theories, like men, "may rise on stepping-stones of their dead selves to higher things." Finally the truth is elicited. While avoiding dogmatic statements, I hope to show that the application of experiment to the study of cancer is rational to-day, and has advanced in four or five years to a stage where the results have become of constructive value.

In the space of a short article it is impossible to give an adequate account of the many aspects from which "cancer" requires to be studied. I propose to consider mainly the application of the experimental method to the study of growth, and to show how greatly knowledge has advanced since the first experiment on cancer was made in 1773. At that time

experiment was guided by reasoning from entirely erroneous premisses. For a long time subsequently, knowledge was greatly advanced by descriptive investigations undertaken with the assistance of the microscope. Later, experiment was resorted to again, in applying the methods of bacteriology, with results which showed rather what cancer was not, than what cancer was. Biological knowledge required to advance in other fields before the experimental method could be so applied to the study of cancer as to yield positive contributions, carrying us forward from where clinical, histological, and bacteriological studies had reached their limitations, and from where physiology and chemistry could find no point of attack.

The Academy of Sciences, Belles Lettres, and Arts at Lyons proposed the following as the subject of a prize dissertation for the year 1773: "To form such inquiries on the causes of the cancerous virus as may lead us to ascertain its nature and effects, and best methods of obviating it." The foul sloughy discharge, the "cancerous virus," proceeding from ulcerating, septic, "open cancers," was at that time held to be the characteristic of the disease, and the subject selected was the direct incentive to the first experiment on cancer.

The prize was awarded to Bernard Peyrilhe, who remarks, in the course of his essay, "With respect to the contagious nature of this virus, it must be acknowledged that, either externally or internally applied, it is capable of infecting the healthiest of men." . . . He found that by the subcutaneous injection of what he regarded as the "cancerous virus," he could reproduce those clinical features which were at the time supposed to be characteristic of the disease. The correspondence seemed to him, and to the judges of the prize, to be so close as to merit the inference that he had communicated cancer itself, although the experiment terminated prematurely. His essay was ordered to be published by the Academy. It attracted so much attention that it was translated into various languages, and influenced medical opinion for many years. The experiment really bore on the transference of secondary bacterial infections, and not on the transference of cancer. The experimental investigation of cancer is to-day something entirely different. The *sine quâ non* to its satisfactory pursuit is the fulfilment of the requirements insuring absolute asepsis. The animals which are made to bear cancerous growths artificially, suffer little or no incon-

venience; since secondary bacterial infections are inimical to the objects of the experiments, they are carefully avoided. As will be explained below, the transference of cancer differs fundamentally from the transference of any known infective disease.

Peyrilhe's experiment may, however, be held to have been positive, in that he had produced artificially what were then regarded as the particular features of the "cancerous virus." The repetition of Peyrilhe's experiment to-day could not be justified as a means of throwing light on the nature of cancer. Peyrilhe was under the influence of Descartes' lymphatic theory, as were his contemporaries Alexander Monro and John Hunter in this country. He was ignorant of the true structure both of cancer and of the healthy tissues, and the "cancerous virus" itself was nothing more than the consequences of the action of the organisms of putrefaction on the tissues. It was not till one hundred years later that Lister's experiments on wound infections demonstrated conclusively that this was so.

Progress was about to be made along unsuspected lines, and during a century the valuable additions to knowledge of the nature of cancer remained almost entirely descriptive. The developments of normal and pathological anatomy, of histology and of experimental physiology, riveted attention. They yielded, as the end result, criteria of the minute structure and nature of cancer absolutely different from those by which the success of Peyrilhe's experiment had been tested. The "cancerous virus" survived; but had already acquired a changed and vaguer connotation, when, in 1840, Langenbeck found solid nodules—new formations of tissue—develop in the lungs of animals after inoculating them with cancerous *tissue* from a human breast. Those nodules were taken to imply that the animals had become infected from human cancer, as the nodules in Villemin's experiments (1865) were interpreted—as we now know, correctly—to mean the infection of rabbits by the inoculation of tuberculous matter from the human subject.

The significance of the many resemblances of cancerous to healthy tissues was still unappreciated. It was long in being fully comprehended. Its importance received occasional emphasis early in England, *e.g.* by Pott, Abernethy, Wardrop, Astley Cooper, Walshe, Hodgkin, Everard Home, Carswell, Wilks, and others, and was fully recognised by Johannes Müller and his pupil Virchow. In 1868 Wilks emphasised how this similarity

differentiated the disease from infections. Thiersch, Waldeyer, and others finally established the relation of cancer to normal tissues, and its probable origin from them in many cases, in opposition to the humoral theories which found their last exponent in the distinguished Virchow.

Experiments like Langenbeck's were repeated with great perseverance even up to the present decennium; but, with the development of bacteriology, they were modified in many instances, where the experimenter believed he had discovered the "virus" or other minute parasitic cause of the human tumours. Whereas many observers were unable to induce cancer in animals in those ways, others claimed success. Criticism always effectively disposed of those claims. The tumours produced in animals bore vague, or even only imaginary, resemblances to the tissues of the human tumours employed in the experiments. Many were proliferations of the inflamed tissues of the animals themselves, as the result of the experimental inoculations, while others were normal and pathological structures encountered in animals, but not in man, and entirely independent of the experiments.

All this time descriptive pathology and study at the bedside were advancing knowledge, leading ultimately to the accumulation of an overwhelming amount of evidence in favour of conclusions in two directions: (1) the cancerous tissues destroyed life mainly, if not solely, by their powers of progressive proliferation and of dissemination in the body: (2) the proliferation arose primarily in a circumscribed area, and proceeded from causes inherent in the growing cells themselves. It required many years before the early surgical treatment of the disease ousted all other methods, and was acknowledged to be justified absolutely by increasing certainty of the circumscribed origin of cancer. This had been clearly enunciated by Wilks as a result of investigations pursued between 1847 and 1868, and was stoutly defended by Campbell de Morgan and Charles Moore, against the constitutional views of the disease ably expounded by Paget and his followers. The opposing schools joined issue in a memorable debate before the Pathological Society of London in 1874. The methods of descriptive pathology and of clinical study ultimately reached their limitations, for they were inadequate to explain the powers of growth, which they had sufficed to

define as embodying the essential problem of cancer. So distinguished an observer as Campbell de Morgan confessed that "experiment fails us, and we know nothing of the earliest stages of the disease." The search for a specific cancer cell proved futile, according to Wilks, as early as 1868. Investigation of the minute intra-cellular structures provoked much controversy during the last twenty years of the nineteenth century, but remained, as it remains to-day, barren of positive results. Discussion of the infective or non-infective nature of cancer became entirely hypothetical. All attempts to induce cancer in animals by inoculation from the human subject having led to negative results, the method had been practically abandoned. Efforts to elicit experimentally the hypothetical (latent) powers of growth of embryonic tissue in support of Cohnheim's hypothesis, or those of groups of adult cells whose "organic continuity" with the tissues was dissolved, as postulated by Ribbert, showed how limited were the powers of growth of embryonic and adult tissue. In the case of embryonic tissues they showed also that the ultimate cessation of growth was accompanied by a differentiation into tissue of adult type.

The acquisition of new knowledge seemed very remote indeed. In spite of the most discouraging outlook, courageous and serious resort to experiment had become a pressing necessity at the end of the nineteenth century, and, fortunately, the success attending subsequent experiments has conferred a positive value on much of the apparently negative experimentation described above.

The study of the phenomena called forth by inoculating the tissues of animals into others of the same, and of alien species, showed during the closing years of the last century how distinct —chemically and biologically—the tissues of one species of animal are from those of another, even when nearly allied and elaborating their tissues from identical pabulum. The demonstration of the difference appears to have re-directed attention to a few earlier experiments on the transmission of tumours from one animal to others of the same species. Statements of the success attending the deliberate inoculation of human beings with portions of their own cancerous tumours were remembered. Observations made by Hanau, Jenny, Morau were remembered as indicating the transference of the disease from rats and mice to others of the same species.

It was by no means clear how those experiments were to be

interpreted, nor how the disease had been transmitted, and they had been received with scepticism apparently justified by repeated failures to transmit human cancer to animals. The recollection of them was born of the despairing hope that, perhaps, after all, statements relating to cancer in animals had been unduly neglected. It had been asserted frequently that the disease was peculiar to man, even to civilised man, that it was rare in other races of mankind, and in the domesticated animals with whom he came in contact, but altogether absent in aboriginal races and in wild animals. It is only fair to add in passing that veterinarians had described all the main types of cancer in the domesticated mammals.

At the time of the foundation of the Imperial Cancer Research Fund the position was briefly as follows: The gradual exhaustion of the methods in vogue had led to a cessation in the advancement of knowledge on the nature of malignant new growths. The bedside observation of cases in the human subject, combined with anatomical, microscopical, and chemical examinations in laboratories attached to hospitals, had advanced to a stage where they seemed to raise more difficulties than they solved. As in the corresponding stages of previous attempts to solve other anatomical and physiological problems, the number of contradictory speculations current was legion. They were based on the same observed facts, which were being added to continually by other facts of the same kind—*i.e.* there was vain repetition. The exact knowledge of the disease was strangely restricted to its occurrence in the more civilised races of man, while the explanations of the observed facts roamed over the full field of medical and biological knowledge, and speculation. This discrepancy required adjusting. The impossibility of directing speculation into proper channels, or even of determining what those channels might be, by other methods, caused the need for comparative studies and for experiment to be acutely felt.

The first organised attempt to broaden the basis of the knowledge of cancer, and of its experimental study, was made when the investigations of the Imperial Cancer Research Fund [1]

[1] A "Society for Investigating the Nature of Cancer" was formed at John Hunter's instigation in 1804. The German Cancer Committee was founded in 1900; its work was, however, directed to applying statistical methods to prove the infective nature of cancer. The New York State Cancer Laboratory at Buffalo was in working order in 1899, the work has been almost entirely experimental; but mainly directed to search for evidence in favour of infection.

took definite shape on the basis of a scheme of research submitted to the Executive Committee by myself in October, 1902, and diligent search was instituted into the occurrence of cancer not only in all races of mankind, civilised and aboriginal, but also throughout the animal kingdom. A farm was secured for observations on the larger domesticated animals suffering naturally from cancer, and every opportunity was utilised of testing the possibility of transferring the disease and studying it under experimental conditions. The scheme of experimental research, thus embarked on, received an unexpected justification and a great impetus by the publication of Jensen's accurate and fundamental observations on the inoculation of a tumour of a mouse in 1903, and contemporaneously of those of Borrel. Since then valuable work has also been done by Apolant, Haaland, Loeb, Michaelis, Henke, and, above all, by Ehrlich.

Jensen's great service consists in the fact that he did not restrict himself to demonstrating the reproduction at the site of inoculation of the features of the original growth. He also proved,[1] by carefully following the processes at the site of inoculation step by step, that the new formation was due to the continued growth of the cells peculiar to the tumour, parts of which he had introduced. Jensen's work has been energetically followed up in all civilised countries, and in the first instance in the laboratory of the Imperial Cancer Research Fund.

The investigations of Murray and myself on an adenocarcinoma mammæ and Jensen's own tumour confirmed his observations, and, by extending them to a large number of other malignant new growths in mice, established the experimental study of cancer on a secure foundation; so that, after some preliminary controversy, it is now universally agreed, infection plays no part in the process of experimental transference. On the contrary, transference to fresh mice merely affords the cancer cell an opportunity for continuing to proliferate in fresh soil. With Murray I made an exhaustive study of the processes at the site of the inoculation of cancerous tissue in the case of

[1] This demonstration is sometimes erroneously attributed to L. Loeb, who obtained tumours on inoculating sarcoma in rats in 1901-3. Loeb's original description of the processes at the site of inoculation does not bear this interpretation. He also admitted the possibility of the tissues surrounding the grafts acquiring sarcomatous properties.

twenty sporadic mouse tumours, and conclusively proved that the cancer cells are merely transplanted into the new animals which provide them with nourishment, by means of a specific connective tissue reaction supplied afresh after each fresh transplantation.

The criticism, that the tumours experimented with were not comparable with cancer in the human subject, was advanced as speedily as of yore, and with all the assurance born of a knowledge of its effectiveness in discrediting earlier experiments. It is still feebly uttered by certain persons who lack extensive experience of cancer in animals. At last, however, it was to be met satisfactorily. Before proceeding to the study of other problems, Murray and myself spent much time in demonstrating, not only that the starting-point of the experiments has been cancer of the mamma, but were at great pains to reproduce artificially metastases, infiltrative and expansive growth—in short, all the main features of the disease in previously healthy animals. With Cramer we drew a parallel between the growth of cancer under natural and experimental conditions. Haaland independently did the same for a number of carcinomata, and demonstrated that Ehrlich's experimental sarcoma formed metastases, and behaved in other ways like a malignant new growth of the human subject. Apolant published an elaborate and valuable monograph on the histology and pathology of the mammary tumours of the mouse.

These results are based on observations all but limited to the mouse. As yet our numerous inoculations of cancer in other vertebrates have met with only transitory success in rats and in a single carcinoma mammæ of the dog. Even in the case of mice there are great difficulties to be overcome: for the other vertebrates many of the difficulties are still unsurmounted. The failures may be due largely to the relatively small number of inoculations made as contrasted with mice, as well as to difficulties associated with varying suitability of the animals employed, which the study of the transplantation of cancer in mice has proved is a factor of great importance.

The inoculation of cancer in mice has been necessary on a scale perhaps unprecedented in the experimental study of disease, in order to prove that the cancer cell is able to grow and to proliferate continuously in animals of the same species only. To establish that the cancer cell is not transferred

naturally from one individual to another, equally extensive observations have been necessary. As I shall show later, the cancer cell of the mouse is in all probability a mouse cell incapable of nourishing itself and proliferating, except when in intimate organic union with the body, and nutrient supply, of the living mouse. Ehrlich has shown that a transitory growth follows the transplantation of one of his mouse tumours into rats. We found that the same power is possessed by other mouse tumours. Growth, however, speedily ceases in rats, although it is retained unimpaired if the cells be re-transferred to mice after a short sojourn of six to eight days in the rat's body. A mouse tumour does not grow equally well in all mice. We found difficulty at first in getting Jensen's Danish tumour to grow in English mice, and Michaelis and others have entirely failed to get it to grow in the mice of Germany, England, and other countries.

The progress made by the demonstration, that cancer could be transplanted and artificially propagated *ad libitum*, was not of the obvious kind appealing to the multitude. If transference had proved that the tissues of the new animal acquired cancerous properties, *i.e.* that the disease could be conveyed by way of infection, our knowledge of its nature would have been advanced enormously at one step. Then investigation could have been legitimately limited at once to identification of the agent and of the channels of infection.

The nature of the transference of cancer was out of accord with all known processes of infection, in this respect merely presenting old problems in a new light, as well as new problems for solution. However, Murray and myself were able to draw certain conclusions other than those drawn by Jensen, which have been abundantly confirmed since by others: (1) The amount of proliferation exhibited is enormous, once the primary difficulty of transplanting a mouse tumour at all has been overcome. The proliferation is then out of all conformity with the laws of growth in vertebrate organisms. The cancerous tissue retains its histological characters. (2) If a large number of healthy mice be considered, growth proceeds readily in mice in which cancer is rare naturally. Although the maximum incidence of cancer occurs in the later years of life, growth proceeds as well, and even better, in young animals than in old. Therefore, if senescence is intimately bound up with the

origin of cancer, it is unnecessary for growth to continue. (3) The conditions of the origin of cancer were to be sharply distinguished from those of continued growth. (4) The progressive, apparently vegetative, growth was to be explained as inherent in the cancer cells without the assumption of the stimulus of extraneous agents. The amount of growth presented a cell problem of importance in itself and required to be further analysed. (5) The purely cell problems of cancer required to be attacked by the methods of experimental and comparative biology rather than from the narrower standpoint of human pathology.

Those conclusions would have been illegitimate if drawn only from experiment at that time. They were advanced also on the basis of a comparative study of the disease in the vertebrates down to marine teleostean fishes living in a state of nature, and after careful statistical studies of the national mortality from cancer, and of its occurrence in the patients of London hospitals. The zoological distribution of cancer made it obvious that it developed in man, independently of any direct influence proceeding from civilisation, diet, or other one of many inconstant external factors. Subsequent studies in the same direction, and also into the ethnological distribution of the disease, have but rendered this inference more justified. The disease has been found in all those races of mankind among whom diligent search has been made. Where it was said to be rare it has been found to be common—*e.g.* in Japan some 25,000 deaths are annually recorded from cancer. Where it was said to be absent it certainly occurs. Of course, no comparison or statement of relative frequency is possible between civilised and aboriginal man, and between tame and wild animals. The fact of prime importance is that the disease is of universal occurrence, pervading all forms of vertebrate life, and everywhere adapting itself to the conditions presented by different species. The disease is universal, but the difficulty of transferring it even to individuals of the same species is unique, and when successful is not to be confounded with the production of cancer *ab initio*.

Throughout the entire distribution of the disease two facts stand out prominently: The number of cases recorded is in direct proportion to the care with which it is possible to make examinations, and to the number of adult and aged individuals

examined. That cancer develops with increasing frequency with advancing years in all animals, whether their lives be long as in the case of man, or limited to two or three years as in the case of the mouse, is a biological law of universal application. The only class in which cancer has not yet been found, viz. the reptilia, is the exception proving the rule, for in them life may extend to hundreds of years, and the opportunity for examining a sufficiently large number of aged reptiles does not exist. The same applies, if in lesser degree, to the apparent rarity of the disease in wild animals generally, since they do not naturally survive the functional activity of their teeth or their reproductive system.

The greater recorded frequency of cancer in domesticated mammals as compared with wild animals implies, not that the disease is communicated from man, but simply, that man protects them and provides for them, so as to permit of their attaining their respective cancer ages.

In the case of the organs of the human body, cancer exhibits a corresponding dependence on the duration of life, *e.g.* chorion epithelioma develops before birth and presents a perfect parallel to the incidence of cancer in short-lived animals. In a general way it may be said, since space prevents my discussing details, other organs present all gradations up to the skin, which is functional so long as life lasts, and in which the maximum incidence of cancer is only attained in extreme old age. The age of the individual organism is of less moment than the senescence of its several tissues in determining the incidence of cancer. Hence cancer may occur at any age, in the new-born, and even before birth. As a matter of fact it is more frequent at birth than between the tenth and fifteenth years of life. It is therefore wrong to assert that cancer is caused by "old age."

The generalisation as to the constant association of the incidence of cancer with senescence adds greatly to the significance of its unbounded proliferation, when propagated by transference from one set of mice to another *ad infinitum*, since the size of the body and of its individual organs, as well as the length of life, are specific for each species of animal. They distinguish different species as sharply as any of the other criteria on which the systematic zoologist depends for his classification, *e.g.* as sharply between the mouse and the rat as between the mouse and the elephant. As I shall describe below,

cancer frequently stops growing, and this is the most encouraging result obtained by experiment. Nevertheless, there is as yet little reason to suppose that limits corresponding to those set to the growth of organisms and their organs, are necessarily set to the growth of cancer in any of the vertebrates, except when artificially set by the death of the animal in which it originates or is growing. The primary transplantations of our sporadic tumours have succeeded for 66 per cent., and ultimately all may be found to be transplantable. Hence, since a mouse tumour has now been growing twice as long as a mouse lives, the more limited evidence of a similar phenomenon in other vertebrates, *e.g.* rats and dogs, is probably due mainly to insufficient experimentation, and to failure to supply suitable soil. On the one hand, we have the limited powers of proliferation of normal tissues which never produce tumours when transplanted, and the unlimited proliferation of cancerous tissue; on the other hand, we have the dependence of the inception of cancerous change on senescence of the tissues as determined by the laws limiting the duration of life specifically. We have stated that in this association lies the crux of the problem of cancer, and R. Hertwig in referring to physiological senescence, and others, have also noted its biological importance. This association involves a problem which cannot be attacked directly at present, because we are still unable to determine the inception of cancer experimentally. We can, however, approach it indirectly by the prolonged study of the growth of cancer when once it has started, and endeavour to determine if it be purely vegetative, dependent entirely on the supply of adequate and suitable food, or be perhaps also maintained and renewed by some intra-cellular reorganisation occurring periodically, at a time when growth tends to cease naturally. In short, we must find out if the study of growth gives us any clue to its nature and origin. We can also study the conditions favouring and retarding its continuation or modifying it. Thus, the experimental study of cancer is at present essentially the experimental study of the growth of cancer; but this is no subsidiary attribute—it is in reality that property of cancer by virtue of which it destroys human life. It is customary to consider the growth of tumours as expansive or "benign," and infiltrative or "malignant," a classification corresponding also to their clinical behaviour. As a matter of fact

the two forms of growth are interchangeable experimentally. For different carcinomata Murray, Cramer, and myself have shown that this interchange of the mode of growth is dependent on the anatomical surroundings of the tumour, and not on an alteration of the properties inherent in the tumour cells. It therefore suffices to study mere growth, and in doing so one may disregard the features of most use in the current classification of tumours.

The transplantation of a sporadic tumour is effected according to our method as follows: The tumour is removed from the animal so as to avoid bacterial contamination, and weighed. It is divided into portions which are placed in separate receptacles. The portions are then inoculated by means of hypodermic needles, minute fragments (*circa* 0·01—0·03 grm.) being broken off and inserted subcutaneously. The tumour is thus distributed over as large a number of mice as possible—it may be fifty or four hundred. The experimenter must then possess his soul in patience. Rarely is he rewarded by the appearance of true tumours, at the site of inoculation, within a fortnight. He may have to wait from three to six months before the inoculations can be pronounced to have fallen out either positively or negatively.

The nature of the result is determined mainly by two factors: variations in the suitability of the soil the mice afford for the growth of the grafts introduced as above; and variations in the character of the tumour cells, not only of different tumours, but of one and the same tumour. The suitability of the soil may be taken to be fairly constant when large numbers of young mice of the same age (six to eight weeks) and of the same stock are employed. Adult and old mice are not only much less suitable than young animals, but they also exhibit greater individual idiosyncrasies. Normal mice may be said to offer a certain unsuitability, or to be resistant, to inoculation, when tumour cells are transferred to them after removal from their natural environment in the animal in which they developed. This resistance acts as a sieve, sifting out the tumour cells which are unable to nourish themselves and proliferate in this new and, it may be, very strange environment. Thus the positive results of the primary transplantation seldom form a high proportion of the animals inoculated. They are probably obtained by the segregation of groups of cells of high assimilative energy and

growth, in mice whose resistance is below the average, or rather the suitability of whose soil is above the average. A summary of some observations we have already published will serve as an illustration. The final results of transplanting 32 spontaneous tumours of the mamma show that 2,278 of the mice inoculated remained alive three weeks later, and 72 of them ultimately developed tumours—*i.e.* only 1 inoculation out of 31 was successful, or 3·2 per cent. A tumour is propagated by a repetition of this process of transplantation from one series of mice to another. But the subsequent transplantations are only exceptionally accompanied by better success. In illustration of the pertinacity necessary in such experiments, I may state that it was not till we had repeated the primary process above described for twenty-seven different sporadic tumours, and also repeated it for each tumour one, two, three, and four or more times, that we alighted on a growth capable of unlimited propagation. This difficulty in starting propagation illustrates merely one aspect of the initial obstacles which those who embarked on the experimental study of cancer have had to overcome in the case of mice, and are still striving to overcome in the case of other animals.

When once a tumour has been got to grow well in mice of a particular race, similar difficulties are often encountered in transferring it to mice of strange race. Thus we added the study of Jensen's tumour, which was accustomed to Danish mice, to those discovered by ourselves with the greatest difficulty. Michaelis and other investigators have failed altogether to get Jensen's tumour to grow in strange mice. We failed also to propagate a tumour sent from Paris by Borrel. Our experience leads me to surmise that those absolute failures may have been due partly to an unfavourable phase of growth of the cells of the tumours. Our initial success with Jensen's tumour was only $4\frac{1}{2}$ per cent. of the inoculations.[1] When the tumours grown in English mice were transplanted again into English mice, the percentage soon equalled that obtained by Jensen in Danish mice, and in single experiments greatly exceeded it,

[1] The tumour had been removed from a mouse, was forwarded by ordinary post hermetically sealed in a glass tube, and transplanted into English mice five days later. Our primary transplantations were therefore made with an added difficulty, but they also illustrated the vitality of the tumour cells after separation from the body.

rising to 90 per cent. at the third transference. When once the initial difficulties have been overcome, the growth exhibited by propagated cancer, as illustrated by several of the tumours we have studied, soon passes beyond the bounds of all measurement. A small piece of tissue weighing no more than 0·01 grm. frequently increases to 1·5 grm. of tissue in ten days. This is an increase of over a hundredfold, and under suitable conditions 90 to 100 per cent. of the animals develop tumours through many successive transplantations. This sequence of events is not constant when tumours can be transplanted successfully.

Some sporadic growths grow well from the outset of propagation. For others a marked increase in the success of transplantation is observed, frequently after three or four transferences. For others again the percentage of successful inoculations cannot be raised to, or maintained at, 100 per cent.; but remains constant within certain fluctuations. However, for the majority of our carcinomata growth ceased at the third or fourth transference. We have interpreted those differences to signify primary differences in degree, inherent in the cells of different tumours. They persist during continued propagation in the majority of cases; so that each tumour exhibits from the outset of propagation a constant behaviour within limits. We have refrained from terming the increased success of transplantation occurring in special cases "an increase of virulence," as has been done by analogy with what occurs when bacteria are propagated by the method of *passage* from one animal to another. The term "virulence" should be dropped and "adaptability" substituted, because the method of propagation is essentially an artificial selection of the most rapidly growing tumours, and their subdivision and distribution over a large number of animals. Although the greater success sometimes attending later inoculations suggests an alteration in the energy and rate of growth of the tumour cells, the phenomenon referred to may be explained without having recourse to this assumption: (1) by an increase in the number of proliferating cells, similar to what occurs in the propagation of domesticated animals as in the following example; and (2) by adaptation.

The increase in the numbers of any form of fancy dog which happens to become fashionable is due not to an artificial shortening of the period of canine gestation, but to increased breeding facilities, *e.g.* to multiplication of the number of those

who find it profitable to breed that kind of dog. There is a multiplication of the number of dogs breeding, so in the artificial propagation of cancer we multiply the number of cells proliferating. I discuss later the possibility of biological alterations leading to increased rapidity of cell growth. Propagation segregates in the first instance the cells which can accommodate themselves to the artificial conditions, and then provides for their nutrition and proliferation. Thus there are more of the suitable cells in each of the later grafts, and within a given period, this primary advantage gives bigger tumours from each single graft, and a higher percentage of tumours over the total number of animals inoculated.

A violent change in environment is effected when a tumour is removed from the animal in which it developed. The manner in which the change is effected is important. Whereas we have succeeded in transplanting 66 per cent. of the sporadic growths we have discovered, Ehrlich has transplanted 14 per cent. of his tumours successfully. The discrepancy is certainly due to the difference in method. As a rule only the tumours best suited to propagation survive Ehrlich's procedure, while we have obtained a broader basis for the study of the growth of tumours, since our material includes tumours of all degrees of transplantability. One group of tumours does not survive the process at all. A second group grows for a variable time and then dies, being unable to adapt themselves to a strange and presumably an unfavourable environment. The tumours of a third group are able to adapt themselves gradually. The fourth group adapt themselves quickly or at once, and this is the small group which are easily propagated. It is possible that among them there are tumours surviving transplantation, not only because of the inherent properties of their cells, and their capacity for adaptation, but because the change in environment is in reality to a more favourable soil. In the third and fourth groups there must be also more and more cells suited to propagation in the grafts at each additional transference, till a maximum is reached. Although the group of tumours giving maximal success on propagation are of practical importance in experiment, because of the ease with which they permit of controls to attempts to modify growth, their theoretical value depends on their relation to the varied degrees of energy of growth exhibited by the whole group of tumours. It is

obviously of importance to determine experimentally whether or not all tumours tend to augment their energy of growth to the maximum exhibited by this group, and at the same time to assume the same histological garb. At present many tumours appear to retain their own peculiarities, and although the energy of growth may increase, it is not yet possible to determine whether or not the tumours of one organ ultimately approximate to one form when growth is prolonged sufficiently.

I may point out here that the first and second groups of tumours behave on transplantation as embryonic and adult tissues do, by exhibiting limited powers of proliferation, with the difference between cancer and embryonic tissue, that the former does not differentiate into an adult form. We are therefore able to place a positive value on the negative efforts which have been made to produce tumours by propagating normal tissues, and we are able to establish all gradations from the limited growth of normal tissues under experimental conditions, up to the remarkable phenomenon exhibited by the unlimited growth of the cells of some cancers under the same conditions. Thus experiment has bridged over the gulf between normal and cancerous tissue so far as their powers of growth are concerned. The limited growth of normal tissues, when transplanted, is independent of any extraneous organism. There is no need to assume such a dependence when cancerous tissues exhibit corresponding limitations; and if not, why should it be necessary to assume this intervention when the powers of growth pass insensibly through all gradations to those of unlimited amount?

The possibility of an accelerated *rate* of proliferation may be entertained when a tumour has been continually transplanted during long periods, as in the case of Jensen's tumour. If I understand Ehrlich rightly, this is what he means when he states that the increase in "virulence" is due to the avidity of the receptors having attained a maximum in consequence of rapid passage from animal to animal. I shall show immediately that there are natural fluctuations in the amount of proliferation. In the case of rapidly growing tumours all the inoculations which are successful yield tumours quickly (within, say, ten days). Mice then negative remain so. The fact shows that rapidity of proliferation is closely bound up with an extreme susceptibility to nutritive requirements. Since growth presents

natural variations, an increase in its rate may be one result of our artificial selection in long-continued propagation. In passing I may merely mention it is now well established that the amount of proliferation can be influenced in the opposite direction—viz. diminished by exposure of a tumour to heat. The environment may be of great importance when a tumour is propagated for years. Theoretically the long-continued growth of cancer cells in the soil provided by the mice of one stock or country may handicap them for growth in the different soil provided by mice of another; but, whether this be so or not, augmented adaptation to an accustomed soil may result in an enormously increased proliferation. In this direction therefore the cells of later generations may be biologically very different from those remotely antecedent. What occurs when a tumour is propagated by transference through many generations of mice is determined not so much by the number of transferences, as by the long duration of the particular environment, breeding as it were a cell of particular quality. If one follow the process of artificial propagation back step by step to the primary animal, there is no reason why one should stop there, since the gulf between the growth of cancerous tissue and normal tissue after transplantation has been bridged over. What takes place in artificial propagation may well be but an artificial reproduction of what had long been going on naturally in the animal in which cancer developed. However, it is inadvisable to pursue such speculations further at present, for the conditions of the growth of cancer in the spontaneously attacked may be different from those in normal animals, although the lesions are the same. At any rate, the differences between individuals may be of prime importance in determining the nature of growth in the primary transplantation as well as in the individual spontaneously attacked. It seems, at least, that the preceding considerations give us a deeper insight into the nature and clinical behaviour of the cancers of man during their continued growth, and when they exhibit what appears to be a change to a more malignant condition.

The phenomena of growth can all be explained without the assumption of microbic interference. And this brings me to the further consideration of some matters of clinical importance. When the growth of a tumour under artificial propagation is

contemplated as a whole, fluctuations in the rate and amount of growth are observed, even when many batches of the inoculations yield 90 to 100 per cent. of tumours. These fluctuations can be considered from two standpoints: either they are due to variations in the suitability of the mice inoculated, or to others inherent in the tumour cells. While variations in the suitability of the mice, or even of the same mouse at different times, no doubt contribute to their production, they are insufficient to explain all the phenomena. The fluctuations may be revealed by (1) variations in the success of transplantation, (2) a contrast between the sizes of the tumours in different batches, or even in the same batch, (3) a tumour which is growing rapidly may come to a standstill, diminish in size, subsequently grow rapidly, and again diminish, (4) diminution in size, however, is frequently followed by entire disappearance and absorption of the tumour. Those features of growth can be studied in parallel experiments in such a way as to bring out the probability that they are for the most part manifestations of a variation in the assimilative energy of the tumour cells themselves. In the human subject there are corresponding fluctuations in the growth of cancer. In one part of a tumour growth is proceeding rapidly, in another part slowly. Periods of exacerbation alternate with periods of amelioration. Further, secondary nodules of growth are known to disappear while others are growing, and occasionally primary growths have disappeared. The observations made on mice emphasise the importance of those clinical features, largely discredited, in the human subject, since they have been often interpreted to mean that the growths exhibiting them were not cancer. The experimental propagation of cancer has demonstrated conclusively that mice can recover from artificial tumours. In the elucidation of this process, and of its counterpart in spontaneous cancer, lies the hope of assisting the surgeon. At present I can only foresee a still remote possibility that dissemination from the primary focus may be hindered; I can foresee no probability that the primary focus will be got rid of by other means than early surgical removal.

The ultimate absorption of transplanted tumours requires to be considered in relation to certain other facts. The mice in which it has taken place are protected highly against subsequent inoculation with the same growth, and to a lesser extent against

other growths. There is thus a degree of protection which is common, and a certain degree which is specific. The spontaneous disappearance of tumours occurs, entirely beyond our control as yet. But the protection it confers can be imitated artificially. The same degree of common protection can be conferred by the preceding inoculation of tumour material if followed by no growth, *i.e.* if absorbed, and this is not so remarkable as the fact that it can be induced also by the injection of the normal tissues of the mouse and most readily by normal blood ; but not by the cancers or tissues of alien species. The far-reaching significance of the protection which can be induced by carcinomatous, by sarcomatous, or by normal tissues, causes me to emphasise that our observations and Ehrlich's are in essential agreement. We require to learn whether the protection thus conferred is actively induced or only passively conferred. In the case of blood this question was most easily settled. The protection is not passively conferred by the serum, but is actively induced by the blood cells. To sum up, we are able to so modify the soil provided by mice that cancer cannot grow in it. For indications of the change we are dependent on the behaviour of the living cancer cell in the living mouse; we are dependent on experiment absolutely.

Jensen recorded the disappearance of tumours in 1902-3. The first occasion on which we noticed a large transplanted tumour disappear was while studying a batch of mice with his tumour in August 1904. This tumour was exhaustively studied, and the important part phagocytosis played in the process discovered, not only in the case of this entire tumour, but in more limited areas of a very large number of tumours. We have since recorded the same process for other carcinomata, and its importance has been emphasised by others, especially by Clowes. We have observed the same process in localised areas of spontaneous tumours. There can therefore be no doubt that the animal primarily attacked attempts to protect itself by the same means as a normal animal after successful inoculation.

The investigation of the nature of protection is bound up with very great difficulties, which are not diminished by the absence of any analogy with what we know of immunity to infective diseases. Up to the present I have spoken of the propagation of the tumours as if it meant a mere culture *in vivo* of the cancer cells. This, however, is only part of the truth.

As I pointed out on a previous page, the cancer cells acquire at each transference a specific stroma, the connective tissue reaction they call forth in the host. A culture of isolated cells has not been obtained, since growth always proceeds in the form of a tissue with intimate vascular supply. We emphasised the distinction thus revealed between the cells of different growths nearly allied histogenetically, and the parallel it presented to the biological reactions whereby blood relationship has been established. At the same time we pointed out its far greater delicacy. In what I have briefly outlined with regard to protection the same delicacy, or specificity, appears. The cancer cell is dependent on the provision by the host of a connective tissue and vascular reaction, if it is to grow into a tumour. It would appear to be a piece of short-sighted generosity on the part of the host to supply connective tissues to subserve merely the needs of the greedy cancer cells, and yet this appears to be the relation which subsists when a tumour is growing well. The question arises, is the connective tissue reaction supplied only in response to the needs of the cancer cells, or is it really protective, as in the case of the similar reactions elicited by the tubercle bacillus or other organisms? When a tumour undergoes spontaneous absorption, the connective tissue reaction does become protective, and the acquisition of phagocytic properties by its cellular elements is the main factor in removing the remains of the tumour. Thus under certain conditions the organism is certainly capable of defending itself very actively through reaction to the presence of the cancer cells, and after the process remains protected. The conclusion that phagocytosis is the only agency by which protection is conferred would in my opinion be unwarranted at present. Spontaneous absorption appears to be frequently associated with a phase of depressed growth of the tumour cells themselves. We do not yet know exactly whether the cancer cells require to undergo changes—either spontaneous, or induced from the side of the host—placing them at times at the mercy of the connective tissue which, at other times, appears to be their willing servant. When a graft is introduced into a protected mouse, little, perhaps no, proliferation follows, and the tissue speedily dies. Whether it is killed by the fluids of the body, or simply starved to death, because it is prevented from exercising its chemiotactic influence on the connective

tissues, is a problem too hypothetical for discussion here; it will suffice to say, that interference with the chemiotaxis of the cells of tumours of different kind would explain the phenomena thus far observed, their specific and their common features.

Is the protection to be interpreted as due to some virus contained in the cancer cell? I think not. We have pointed out how mere inhibition of the connective tissue reaction would suffice to prevent growth, since its specificity indicates a delicacy of nutritive requirements on the part of the cancer cell far exceeding that of any other known biological reaction. We found that protection is conferred on the mouse only by mouse tumour, not by the preceding inoculation of the tumours of alien animals even so nearly related as the rat. One form of mouse tumour protects against another. We found that protection is conferred on the mouse by the normal tissues of the mouse and not by those of strange species. There is thus something common to mouse tissue and mouse tumour which is not common to mouse tumour and the tumours of other animals. The protection cannot therefore be due to the presence in the tumour cells of a virus common to vertebrate cancer. Reviewing our experiments as a whole, I am of the opinion they establish that the cancer cell is really a cell of the mouse organism requiring the same food, the same kind of connective tissue and blood supply, to which it was accustomed in the mouse in which it developed. The only difference it exhibits is a qualitative one, viz. in the powers of growth and assimilation. Fortunately the cancer cell is very much at the mercy of subtle changes in its environment, and it is by taking advantage of this fact that we have been able to prevent its growth in the living mouse.

The study of cancer in man became increasingly difficult in the course of time because of the mere multiplication of facts defying classification. Malignant new growths in man and in animals—even those of any particular organ and histogenetically related—exhibit an extraordinary variety in their histology and clinical behaviour. This variability is made yet more difficult to comprehend by the inconstancy in the behaviour of tumours histologically indistinguishable. Many attempts have been made to group the phenomena, *e.g.* by pushing the histogenetic subdivision of tumours to absurd lengths, by assuming that progressive loss of histological differentiation proceeds *pari*

passu with prolongation of growth (anaplasia), and, for apparently identical tumours, by assuming differences in the soil afforded by different individuals, and also by the several organs of any single individual. At the outset of our investigations, therefore, the growth of cancer under natural and experimental conditions was selected for study, as covering ground common to all the varied manifestations of tumours. The experimental study of the growth of cancer proved the permanence of the histological characters, and revealed that the cells possessed other qualities of a more or less permanent kind, escaping demonstration by other means. At the same time, experiment shed light on the relations subsisting, on the one hand, between the different properties of cells similar morphologically, and on the other hand the soil in which they are situated. Only by experiment has it become possible to study the growth of one tumour in different soils, and, what is equally important, the growth of different tumours in the same soil. In this way the varying clinical and histological features of the cancers of the mouse's mamma, reproducing as they do in miniature all the difficulties encountered in man, have been relegated to subsidiary importance for the present, in favour of the study of the problem of cell assimilation, which, being common to all these tumours, permits us to unite in one general conception all the gradations and mutations exhibited in the growth of cancer. The experimental study of growth has already enabled us to compare tumours together as regards their biological behaviour (clinical behaviour). It has been proved that cancer grows better in young mice than in old; that some mice of the same age afford a more suitable soil than others; that some sites of the body favour growth while others hinder it; that tumours seemingly identical (when examined by the aid of other methods) can be differentiated from one another, since they possess distinct properties by virtue of which they behave differently in the same soil; that one and the same tumour exhibits increased proliferation alternating with diminished proliferation in a similar nutritive environment, and, this being so, the fluctuations in proliferation are possibly expressions of an alternation in the assimilative powers of the cells of the tumours which exhibit them. Experimental propagation further showed that proliferation can be maintained by normal bipolar division and that other forms of cell division are

unimportant. Division being merely the end phenomenon in the growth of the individual cell, what requires study is not the manner in which the cells divide, but the mechanism of cell assimilation and its relation to nutritional environment. These problems have been attacked experimentally by altering the conditions under which cancer is artificially propagated, and, as I have pointed out above, the nutritional environment can be so altered that the cancer cell is unable to grow. The study of the growth of cancer further permits inferences as to the nature of the changes, in cells and in organisms, leading to the inception of the continuous assimilation of which cancer cells are capable.

Murray and myself pointed out the importance of separately considering two factors in studying the growth of cancer—viz. the conditions of origin and the conditions of growth—and we pointed out that artificial propagation enabled us to study the conditions of growth experimentally. Ehrlich has since penetrated more deeply into the relation of these factors by differentiating the primary cell changes in a circumscribed area from the conditions permitting the cells in such an area to grow into a tumour, and by assuming the importance of constitutional conditions favourable to growth. We have pointed out, with reference to carcinoma mammæ in the mouse, that the differences revealed and shown to be retained in artificial propagation indicate primary differences inherent in the cells of different tumours, and that they can be conceived as due either to a variety of causes or to one causative factor acting in varying degree. As our work proceeded, evidence accumulated pointing more and more definitely to the assumption that one primary change occurring in varying degree explained the different behaviour of apparently similar and nearly related tumours; but we are ignorant of how the primary change is elicited. If histological differences be ignored for the present, the only fundamental differences, from the standpoint of growth, are in the energy of assimilation of the cells, and in the chemiotactic influences they exert on the connective tissues of the host which convey the food supply. In accordance with this conception what are abstractly called variations or differences in malignancy between tumours of the same histological type are concretely expressed as differences in rate of growth. The injury to the mouse in which

a transplanted tumour is growing proceeds only from the consequences of growth, and the demands made for nutriment; but as a rule the mice look quite well, and malnutrition progressing to wasting is an occasional and accidental occurrence.

Thus far I have considered only the growth of cells, but we have to deal with the growth of tumours often weighing nearly as much as a mouse. If cell nutrition is so important it may seem strange to say that the mice usually enjoy perfect health. It was necessary to ascertain if the nutritive balance in an animal had been disturbed by the presence of a tumour in any other way than could be indicated by ill-health and wasting. When very young mice are made to bear rapidly growing and large tumours, they often only attain about half the weight of others of corresponding age. When adult animals bear rapidly growing and large tumours they may lose weight, and more than is accounted for by the weight of the tumour. This they speedily make good when the tumours are removed, and the mice then revert to the normal conditions without any detectable sign of their having ever borne tumours. The gastric contents of normal mice after successful inoculation with tumours contain a large excess of HCl during active digestion, as observed by Cramer and myself, and demonstrated by Copeman and Hake, who have analysed the stomach contents of over five hundred mice. This increase in HCl is not to be considered as out of accord with clinical observations in the human subject. There is much evidence, recently added to by the careful investigations of B. Moore, that the HCl is diminished in patients suffering naturally from cancer. I am at present considering the facts on the growth of cancer in *normal* mice. We require more data regarding mice spontaneously affected with cancer. The contradiction between the state of affairs in normal mice artificially made to bear tumours, and patients bearing them naturally, reinforces the warning I have expressed already. The conditions of the growth of cancer are to be sharply distinguished from the conditions of origin, and I have also pointed out that the conditions of growth in mice naturally cancerous, and in normal mice, differ from one another. The contradiction above referred to is probably only apparent, and when it is resolved we may know much more of the deeper significance of the diminution in HCl in those spontaneously

affected with cancer. This increase in the amount of physiologically active hydrochloric acid is to be regarded as a compensatory response to the needs of a normal mouse plus a tumour. No assumption is made in inferring that the increase in hydrochloric acid is required for the digestion of proteids. The increase in hydrochloric acid is in all probability accompanied by increased secretion of pepsin and trypsin, the ferments concerned in proteid digestion, although this is difficult to determine in mice. The increased activity of proteid digestion is easily comprehended. Whereas, in a general way, the combustion of carbohydrates suffices for the output of energy in an animal organism, proteids are essential to the building up of protoplasm, and the building up of protoplasm is proceeding apace in the continual production of new tumour cells.

On a preceding page I have pointed out the specific characters of the proteids which even nearly allied animals reconstruct from identical pabulum, and how the mouse alone supplies the nutritive environment or pabulum suited to the continued growth of mouse cancer. These facts are to be remembered in the present connection, for there is no need to assume that the increase in proteid digestion involves any other divergence from the normal process. No doubt proteid digestion prepares the food-stuffs for absorption into the fluids of the body in the usual way, and for their utilisation by its constituent cells and by the cells of the tumour. So fine an adjustment can only mean that the cancer cells of the mouse and normal mouse cells compete for the products of proteid digestion. In view of what we know of the specificity of these processes of nutrition, on which so much light has been thrown by Starling and Bayliss, this implies that the cells of mouse cancer are mouse cells able to impress their needs for food on the mouse as a whole by their higher assimilative energy. The facts reveal, at any rate, how great are the demands for food which growing tumours make on healthy and young adult animals, and at the same time show that the normal animal responds to these demands at least by increased proteid digestion. These observations are the mere beginnings of the experimental study of the problems of metabolism in cancer, and which are not easy to attack in so small an animal as a mouse, and will be attacked still more profitably in the case of larger animals, *e.g.* the dog. The problems of excretion which may have practical importance

are not capable of easy solution in the mouse. One can use the organism as an indicator of the nutritive needs and metabolic activity of cells, because in studying propagated cancer we have such a large number of tumour cells of the same kind in one animal. Conversely, as I have shown above, we can use the tumour cells as indicators of changes in the animals. So far as these results go they encourage further experimental investigation into the growth of cancer as a problem of cell nutrition, in which the organism as a whole is implicated, although the demand proceeds from a circumscribed area, limited in the first place to a little bit of tissue no bigger than a pin's head at the time of inoculation. It is obvious that this line of inquiry may have ultimately direct bearings on certain aspects of the disease in man; but I must enforce caution in drawing conclusions, and above all warn the layman that I have said nothing in favour of popular views on diet or disordered digestion as causes of cancer.

This is an opportune stage at which to terminate an outline of the firstfruits of the experimental investigation of cancer, to the development of which the Imperial Cancer Research has very materially contributed. In 1905, 137,128 deaths of males occurred in England and Wales above the age of 35; of these 11,908 were due to cancer. In the same year there were 138,477 deaths of females above 35 years of age, of whom 16,875 died of cancer. Therefore of persons dying above the age of 35, one out of every eleven men died of cancer, and one out of every eight women. Is this great frequency as a cause of death to be explained as due to communication of the disease from one person to another? Our experimental investigations have revealed no analogy with any known form of infection. The chance of ultimately dying of cancer is one in eight for women and one in twelve for men above the age of 35. A simple calculation shows the probabilities of the occurrence of one or several cases of cancer in families of whom few or many survive beyond the age of 35. Murray and myself have pointed out that when the full facts are known, the incidence of cancer in some animals will probably approximate to that in man, although the forms of cancer to which different species are most liable may differ. Since the greater frequency of cancer coincides with the later years of life, the span of life of human beings has long been one of the obstacles preventing a final

settlement of the question whether there is or is not a family liability to the disease. This obstacle is inoperative in the case of the mouse, with a short life of two to three years. Statements have been made of the greater frequency of cancer in the mice housed in certain cages, but no account has been taken of the total population of the cages for the period during which the tumours were observed, nor of the sex and age-constitution of the mouse population. In short, the data necessary to justify statements of relative frequency have not been ascertained. To baldly assert that epidemics occur, or that the disease must have been conveyed from one mouse to another because so and so many cases of cancer have occurred in one cage, as has been done in the most positive manner by the New York State Laboratory, Buffalo, U.S.A., is to ignore the rudiments of statistics. By breeding and in-breeding mice of cancerous stock we hope to finally settle the importance attaching to the apparent frequency of cancer in some strains of mice as compared with others. We have long had such observations in progress; but, since statistical studies on the incidence of cancer in animals require to be conducted with all the precautions accurate statisticians employ in dealing with the incidence of cancer in a human population, we are not yet able to institute comparisons between different communities of mice. These observations do not lend support to assertions of infection, any more than do our studies on the nature of experimental transference, and the means whereby immunity or protection may be conferred. The universality of the disease in man and animals, the biological law of its age incidence, the unique character of the proliferation and its continuation on transplantation, the peculiar nature of the measures which protect mice, as well as the intimate relations between normal and cancerous tissue, and the increased digestive activity induced to compensate for the building up of protoplasm in the tumours borne by otherwise normal animals, all point to the probability that cancer arises *de novo* in the individual attacked. This statement may seem to be mere dogmatic reiteration of an oft-expressed hypothesis; but experiment has removed this conception of the relation of cancer to the individual from the realms of hypothesis to the level of a well-considered theory, harmonising many isolated facts, and fruitful as the basis of further inquiry.

Finally I may point out, that if the comparative and experi-

mental investigation of cancer has revealed the fallacious nature of all reputed analogies with known forms of infection, the results obtained are essentially of constructive value. The cell problems being attacked now were unapproachable five years ago, as were also the relations existing between tumours and the organisms bearing them. Having recognised fully, and insisted from the outset of our investigations, that the reproduction of the lesions of cancer in normal animals by transplantation differed from the development of the disease *ab initio* in animals spontaneously affected, I have confined myself largely to describing the growth of cancer in the soil provided by normal animals, and to drawing some inferences as to the conditions obtaining in the development of cancer. I have shown that even in normal animals the soil plays an important part, and a part which can be modified at will. I have indicated that the soil may play an important part in the spontaneous appearance of cancer in individuals. I have also shown that the primary properties of cancer cells differ. Therefore the circumstances associated with the development of cancer require to be considered with reference to the two sets of factors last mentioned.

The extent to which the experimental method has already deepened our knowledge of the properties of cancer cells and of their relations to normal animals renders it probable, that its further application will throw light on the conditions underlying the association of the inception of cancer with the senescence of tissues, and on the increasing frequency of the disease as age advances, throughout the vertebrate kingdom.

THE USE OF THE ELECTROMAGNET IN PETROGRAPHY

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1. Introduction

It is well known that minerals exhibit varying degrees of permeability in a magnetic field, in consequence of which grains of one mineral can often be separated from those of others. In recent years the method of magnetic separation has become very important in the mining world. It is quite indispensable in a large number of ore-dressing operations, in which domain its utility is fully recognised.

In the laboratory also, this method has often been used with great advantage, more especially in the isolation of minerals for chemical analysis. Indeed, the magnet, and especially the electromagnet, must be regarded as a very useful piece of petrographical apparatus. Experience has shown that it is capable of extensive use qualitatively, while in special cases it yields quantitative results which are fairly accurate, particularly in the examination of sands.

Considering the ready and extensive applicability of this method in rock studies, there is scope for surprise that it has not been more widely adopted, for there can be little doubt that, among geologists, the practical utility of the method is much undervalued where not completely ignored. This may be due in some measure to unfamiliarity with the results already achieved. Hence it is proposed in this article to give an

account of what has been accomplished by the many workers who have used the magnetic method of examination in mineral and rock studies, and to call attention to certain meritorious work, especially by Delesse, which seems to have been unduly neglected by writers of text-books. The account will serve to emphasise the utility of the electromagnet in the examination of grains and fragments of rock-forming minerals.

2. Historical Review

During the latter half of the eighteenth century, numerous observations were made by various workers, including Romé de Lisle, Delarbre, and Haüy, on the magnetic polarity exhibited by crystals of magnetite and hæmatite.

Among geologists, H. B. de Saussure early recognised the value of the magnet, and included it in his list of instruments needful to a field geologist. In vol. i. of his *Voyages dans les Alpes*, published in 1779, he discussed, in a most elaborate and interesting manner, the attractive effect of garnets on a magnetic needle, and described a delicate means for observing this effect; Saussure even proposed to use this property as a means of estimating the amount of iron in a garnet. He also dealt with the magnetic influence of mountains as observed by a magnetometer. As an explanation of this influence he put forth the "rock-magnetism" theory, and considered that the cumulative magnetic effect of the ferriferous minerals (hornblende, etc.) of which the mountains were composed, was quite sufficient to account for the effects observed. Further, he indicated the value of the magnetometer as a means of locating bodies of iron ore. ("Cette observation prouve la sensibilité du magnétometre (1) l'usage que l'on pourroit en faire pour decouvrir des mines d'aimant ou de fer": *loc. cit.* tome iv.).

Incidentally, and as an illustration of the way in which modern authors are apt to overlook the credit due to early workers, it may be pointed out that Haanel[1] attributes the discovery of this method of locating iron ores to Wrede (1843). Again, with respect to Saussure's observations on the magnetic disturbance exercised by mountains, as evidenced in the region of the Alps,

[1] *On the Location and Examination of Magnetic Ore Deposits by Magnetometric Measurements*, Department of the Interior, Ottawa, Canada, 1904.

we may note that M. de Lapparent [1] is content to attribute early observations on this matter to Kreil (1849), who also worked among the Alps, and to Locke (1846), who made investigations in North America.

Korda [2] states that as early as 1778 Brugman, of Leyden, had described many minerals as being magnetic, including those which contained iron and cobalt. The same author states that in 1792 Fullerton obtained in England a patent for separating magnetic from non-magnetic materials by means of permanent magnets.

The geologists of this period were familiar with the wide distribution of magnetite in eruptive rocks; they were in the habit of extracting it from crushed rocks by means of a magnet, and of noticing that the rocks which contained it affected the magnetic needle. In 1794 Dolomieu [3] characterised his group of compact basic volcanic rocks as having, among other things, a marked effect on the magnetic needle. He observed that specimens of certain lavas exhibited a well-marked polarity, which was retained by the fragments when the specimen was broken.

In 1800 Bellevue [4] recommended the partial crushing (demi-trituration) of rocks, and mechanical analysis (*analyse mécanique*) of the fragments, including elutriation and treatment with a bar magnet. In this way he made a thorough examination of the leucite-nepheline-melilite-basalt of Capo-di-Bove, making a fairly full record of its mineral composition. He concluded his interesting memoir by stating his belief, that the adoption of the methods he describes would be a potent means of discovering new minerals, and of elucidating the nature of rocks. It is instructive to note the acute observations made by these early workers, and not a little surprising to find that they achieved so much with the limited means at their disposal. Bellevue especially emphasised the importance of examining the sands which had resulted from the disintegration of rock masses.

As if to show that he had appreciated the importance of

[1] *Traité de géologie*, 1906, tome i. p. 106.

[2] *La séparation électromagnétique et électrostatique des minerals*, Paris, 1905.

[3] "Suite de mémoire pour servir d'explication à la distribution méthodique de tous les produits volcaniques," *Journal de Physique*, etc., 1794.

[4] "Mémoire sur les cristaux microscopiques," *Journal de Physique*, tome li. 1800.

Bellevue's hint, Cordier [1] proceeded to examine a large number of sands obtained from the river beds, lake and sea shores, in the vicinity of volcanoes. By means of a bar magnet he separated the magnetite from these sands, and proved it by analysis to be richly titaniferous. Throughout his later work on the volcanic rocks themselves, Cordier used the magnet freely in his researches, and was able to prove the world-wide distribution of titaniferous magnetite as a constituent of eruptive rocks.[2]

The introduction by Sturgeon in 1825 of an electromagnet bent in horseshoe fashion, disclosed the fact that by such means a magnetic field of great intensity could be obtained. Following this method of construction, M. Pouillet, about 1831, had an electromagnet made which was capable of supporting a weight of about 800 kilograms. With it he was able to prove that many substances were attractable by a magnet which were not previously known to be magnetic.

About 1845 Faraday [3] made his famous experiments with the electromagnet, and examined a large number of substances, including some minerals, distinguishing them as paramagnetic or diamagnetic according as they were attracted or repelled by the poles of a magnet.

It is worthy of note that Faraday's paramagnetic substances included manganese, chromium, cerium, and their compounds. The magnet used by Faraday is interesting because of the fact that he used adjustable pole pieces, which enabled him to vary the distance between the poles, and thus to vary the intensity of the magnetic field. ("The poles are 6 in. apart, the ends are planed true, and against these move two short bars of soft iron 7 in. long, 2½ in. wide, and 1 in. thick, which can be adjusted by screws and held at any distance less than 6 in. from each other. The ends of these bars form the opposite poles of contrary name; the magnetic field between them can be made of greater or smaller extent, and the intensity of the lines of magnetic force be proportionately varied": *loc. cit.* vol. iii. p. 29.) Such adjustable pole pieces are very useful as a means of varying the intensity of the magnetic field, in making mineral separations.

[1] "Recherches sur différens produits volcaniques," *Journal des Mines*, No. 124, vol. xxi. 1807.

[2] "De la manière d'être du fer titané dans les roches volcaniques, et du rôle qu'y joue ce minéral," *Journal des Mines*, No. 133, vol. xxiii. 1808.

[3] "Experimental Researches in Electricity," London, 1855.

They require, however, to be somewhat modified, as will be pointed out later.

Contemporary with Faraday, Pluecker[1] examined some minerals and many other substances by means of the electromagnet. He expressed the relative permeability of these substances by a series of numbers, taking iron as a standard of comparison, in somewhat the same manner as Delesse (see below).

While Faraday, Pluecker, and others were directing their attention to the purely physical aspect of magnetic properties, two French geologists, Fournet and Delesse, attended to the matter more particularly with reference to its bearing on minerals and rocks. Fournet's work[2] was directed towards an explanation of the anomalies of terrestrial magnetism. For this purpose he studied the magnetic properties of all the important rock-forming minerals, not overlooking the fact that even the felspars, due to ferromagnetic impurity, often affect the magnetic needle. He distinguished magnetite, hæmatite, and ilmenite as being magnetipolar. Other magnetic minerals he described as showing simple magnetism—*i.e.* they were attracted by a magnet, but gave no evidence of polarity. He discussed the varying magnetic characters exhibited by rocks of different types as well as minerals, and upon this basis proceeded to deal with the general effects of different rock masses (granites, basalts, limestones, etc.) in modifying the earth's magnetic field. It is noteworthy that Fournet did not use an electromagnet in his observations. He relied on the use of a simple permanent magnet, following the methods of H. B. de Saussure and Haüy. Fournet's paper is a compendium of careful observations, and strikes one as being a document of somewhat considerable value. Unfortunately, it appears not to have received the attention it deserves. As an amplification of the earlier work by Saussure, it merits careful consideration by those who are interested in the bearing of petrography on the subject of terrestrial magnetism.

Of all the contributions dealing with the application of the electromagnet to the study of minerals and rocks, those made

[1] *Poggendorf's Annalen der Physik.*, Band lxxiv. p. 321, 1848.

[2] "Aperçus sur le magnétisme des mineraux et des roches, et sur les causes de quelques anomalies du magnétisme terrestre," *Annales des Sciences, Société d'Agriculture, etc., de Lyon*, tome xi. 1848.

by Delesse rank among the most important.[1] It is all the more necessary to emphasise this work by Delesse since it appears to have been hitherto almost completely ignored. He regarded the magnetic power (*pouvoir magnétique*) of minerals as being to some extent a character of specific importance, and made a magnetically quantitative comparison of a large number of minerals. To do this he crushed them, and experimented with grains of uniform size in a field of constant intensity. The maximum weight of such grains adhering to the poles of the magnet, under uniform conditions, was taken as an index of what he called the magnetic power of a mineral. Thus, two minerals had the same magnetic power if, under similar conditions, equal weights of them adhered to the poles of the magnet. If the adhering weight of the grains of one mineral was twice that of another, the magnetic power of the former was twice that of the latter. In short, the magnetic power was proportional to the weight of the adhering grains, and consequently

$$x = \frac{p}{\mathrm{P}}$$

where x = magnetic power of a mineral,
p = maximum weight of adhering grains of this mineral,
P = maximum weight of adhering grains of some standard substance, the magnetic power of which may be taken as unity.

This method of comparison has been stigmatised as primitive and objectionable; but although it cannot lay claim to great exactitude, it is at least simple and feasible, and proves to be a very efficient and useful means of comparison. Especially when we consider the fact that the magnetic field used is not uniform, and that the permeability of a mineral is generally far from constant, it seems clearly undesirable to sacrifice practical utility, in the effort to attain a more than requisite degree of accuracy.

Using this mode of comparison, Delesse examined numerous minerals, taking steel as his standard. The following list is compiled from his results; the number opposite a mineral

[1] See particularly "Sur le pouvoir magnétique des mineraux et des roches," *Annales des Mines*, 1848, tome xiv. p. 429; also abstract of the same in *Annale de Chimie et de Physique*, tome xxvi. 1849.

represents its magnetic power, assuming that of steel to be 100,000:

Magnetite	64,121	Pleonaste	73
Titaniferous magnetite	48,405	Pistacite	49
Ilmenite	5,764	Allanite	47
Pyrrhotite	4,718	Jasper	33
Hæmatite	2,352	Biotite	20
Hypersthene	687	Idocrase	18
Augite	559	Axinite	17
Garnet (hyacinth)	294	Sahlite	14
Olivine	250	Kyanite	12
Hornblende	237	Talc	12
Chromite	136	Aventurine	7
Siderite	120	Andesine	5
Piedmontite	80	Tourmaline (black)	4
Staurolite	77	Oligoclase (sunstone)	4

The above list is a very incomplete representation of Delesse's results. In many cases he compared the different varieties of a mineral, and the results exhibited considerable variation due to differences in composition and the amount of impurity. For this reason, the numbers given in the above list cannot be regarded as being exact in their significance, especially when they are considered apart from the composition and physical condition of the minerals concerned; but they serve to illustrate, in a general way, the variable magnetic permeability among minerals.

Delesse exercised caution in making his comparative measurements, and avoided errors due to variation in current, etc. The inconstancy of the current generated by his battery led him to suggest that it was preferable to use a strong permanent magnet in making observations on the comparative magnetic powers of minerals. He pointed out that a compound horseshoe magnet was quite powerful enough for the purpose, while it had also the great advantage of being constant.

His comments on the peculiarities exhibited by the different groups of minerals are very interesting. These comments were based largely on the view that the chemical constituents of a mineral asserted their separate magnetic effects, even in a state of combination. Thus he observed that the presence of iron, manganese, cerium, and other paramagnetic elements tends to increase the magnetic power of a mineral, while the presence of silica, alumina, lime, water, fluorine, and other diamagnetic constituents tends to diminish it. A broad survey of minerals

lends much support to this view, and it explains many peculiarities somewhat consistently. But it has long been known that the influence of any chemical constituent in determining the magnetic power of a substance is not strictly additive, and is seriously modified by its mode of combination. Thus compounds of copper with the halogens are said to be paramagnetic,[1] although pure copper and the halogens are separately diamagnetic. Alloys exhibit some striking effects: for example, iron and nickel, both of which are powerfully magnetic, are stated to be capable of yielding an alloy which is practically non-magnetic. Such examples, however, appear to be somewhat exceptional. The investigations of St. Meyer[2] show that, as a rule, a compound consisting of two diamagnetic elements is itself diamagnetic, and that a compound consisting of two paramagnetic elements is itself paramagnetic. But the rule does not apply additively in a quantitative sense: for instance, the magnetic power of a compound consisting of two paramagnetic elements is less than the sum of the separate magnetic powers of the two elements. Again, when water enters into the composition of a mineral, it does not exert its full diamagnetic effect. The physical condition of a mineral is also an important factor in determining its magnetic permeability.

Some of Delesse's observations on the magnetic characteristics of the various groups of minerals are worthy of being recounted. The members of the amphibole group showed variation in accordance with the iron percentage. Actinolite exhibited a feebler power than common hornblende; anthophyllite was feebler still, while tremolite was practically non-magnetic. The pyroxene group showed a variation analogous to that of the amphiboles.

He thought the relatively feeble power displayed by biotite might be explained by the presence of fluorine, which he stated to be probably diamagnetic. Pluecker had already shown that the other halogens were diamagnetic. He was surprised at the feeble magnetic power displayed by the chlorites, seeing that they were comparatively rich in iron oxides and poor in silica. As, however, he included water in his list of diamagnetic substances, we might have expected him to attribute

[1] St. Meyer states that this behaviour is due to impurity.

[2] "Magnetisirungszahlen anorganischen Verbindungen," Stefan Meyer, *Wied. Ann. der Physik*, Band lxix. 1899.

the low magnetic power of the chlorites to their state of hydration, containing as they do about 12 per cent. of water. In this connection we may note that the contrast between hæmatite[1] and limonite is a good example of the effect of hydration in diminishing the magnetic power of a mineral. Another example of this is copper sulphate, which is distinctly more magnetic in the anhydrous than it is in the hydrated condition.

Delesse attributed the low magnetic power of black tourmaline to the diamagnetic effect of boron. He observed that the magnetic power of sulphides diminished very rapidly as the percentage of sulphur increased: thus, pyrrhotite ($Fe_{11}S$), with rather less than 40 per cent. of sulphur, was highly magnetic, while ordinary pyrite (FeS_2), with about 54 per cent. of sulphur, was practically non-magnetic. But here, again, we are tempted to remember that sulphur is a diamagnetic element.

Before quitting this consideration of Delesse's work, it is important to remark that he crushed certain French biotite-granites, and, by the electromagnetic method, not only isolated the biotite, but estimated quantitatively its proportion to the bulk of the rock. ("Le mica est faiblement magnétique, cependant les micas noirs-brunâtres le sont assez pour adhérer facilement à l'électro-aimant. Je me suis même servi de cette propriété pour déterminer la proportion de mica qui se trouve dans quelques granites de la Normandie et de la Bretagne qui sont employés au pavé de Paris."[2])

This appears to be the first record of the use of the electromagnet in the isolation of feebly magnetic minerals from rocks, and the quantitative estimation of the same. But the method is evidently only a logical extension of that adopted by the earlier workers, Bellevue and Cordier, for the separation of magnetite.

In 1872 Fouqué published in the *Comptes rendus* (tome lxxv.) an abstract of a memoir entitled "Nouveaux procédés d'analyse médiate des roches et leur application aux laves de la dernière eruption de Santorin."[3]

[1] Excluding those highly magnetic crystals which contain ferrous oxide, probably due to intergrowths of magnetite.

[2] *Annales des Mines*, 1848, tome xiv. p. 479.

[3] For the full memoir see *Mém. prés. par divers savants à l'Académie des Sciences*, tome xxii. No. 11, 1876.

In this memoir Fouqué described what he called a new mechanical process, by means of which he had been able to isolate the felspars of the Santorin lavas. In this process the rock was crushed and the crushings submitted to the action of a strong electromagnet. The iron ores, the ferromagnesian minerals, and the partially differentiated ground of the rock were extracted, leaving a non-magnetic residue of felspar. The apparatus used by Fouqué consisted of an electromagnet put into action by a Bunsen battery, and was essentially similar to the apparatus used by Pouillet, Delesse, and others. Fouqué also appears to have used a dynamo in some cases, as a substitute for a Bunsen battery. His results are very interesting, and prove convincingly the importance of the electromagnet as a means of isolating minerals. By its aid, and in conjunction with other methods, he was able to demonstrate that a given specimen of lava might contain quite a medley of plagioclases. He also proved that two varieties of pyroxene were present, both rich in lime, but differing considerably in the proportions of magnesia and ferrous oxide; also two olivines which differed in the amount of ferrous oxide present.

It is quite clear, however, from the description which has been given of the work done by Delesse and others, that Fouqué, using the electromagnet in his researches, was using an old and not a new process. It seems scarcely credible that Fouqué could have been unaware of the work already done in this field by his fellow-countryman Delesse, and published in a journal so well known as the *Annales des Mines*. Even in the *Minéralogie micrographique* of 1879, in which Delesse's other work is fully recognised, Fouqué's error remained unrepaired, and it has unfortunately been persisted in by later text-book writers.

Doelter,[1] following Fouqué, and apparently unaware of any important results other than those which the latter obtained, applied the electromagnet to the study of rocks and minerals. He wrongly attributes to Fouqué the priority for using an electromagnet in the systematic study of weakly magnetic rock-forming minerals. He makes matters worse by referring

[1] "Ueber die Einwirkung des Electromagneten auf verschieden Mineralien und seine Anwendung behufs mechanischer Trennung derselben," *Sitzungberichte*, Wien, 1882, Band lxxxv. Abteilung i.

us to the already quoted abstract by Delesse in the *Annales de chimie et de physique*, and misrepresents it by telling us that Delesse had only been able to separate magnetite from his rocks. ("Eine ähnliche Methode wandte Delesse zu Bestimmung des Magnetismus von Gesteinen und Mineralien an. Er konnte jedoch dadurch nur den Gehalt von Magneteisen bestimmen, denn dieses war es, welches bei seinen Versuchen entrahirt wurde.")

Like Fouqué, Doelter operated with magnetic fields of different intensities, obtained by varying the number of the Bunsen cells (2 to 8) which he used. In this way he examined many minerals, and gave a list showing the amounts by weight of the crushed minerals attracted to the poles of the magnet from approximately 0·25 gram in each case, varying the strength of the field according to the ease with which the mineral was attracted. This list in some measure resembles that prepared earlier by Delesse, but is much less complete. Further, for comparative purposes, Delesse's method of using a field of constant intensity and a standard for comparison is decidedly preferable to the method adopted by Doelter.

Another, though perhaps less effective method of comparison used by Doelter, was to operate with a field of constant intensity, and to determine the maximum distance from the poles at which grains of uniform size were lifted by the magnet. The results thus obtained are instructive, and are as follows:

	Millimetres		Millimetres
Magnetite	12·0	Augite (Santiago basalt)	3·0
Hæmatite	6·0	Hornblende	2·8
Siderite	5·0	Pleonaste	3·7
Lievrite	4·7	Augite (Vesuvius)	2·5
Almandine	4·9	Idocrase	2·4
Hedenbergite	4·3	Tourmaline	2·1
Augite (Pico da Cruz)	4·0	Actinolite	1·7
Augite (Praya)	3·7	Olivine	0·8
Epidote	3·7	Vivianite	0·6

Doelter also gives another list, as follows, in which those minerals under the same number have nearly the same magnetic value, starting with the most magnetic and ending with the least:

1. Magnetite.
2. Hæmatite, ilmenite.
3. Chromite, siderite, almandine.

4. Lievrite, hedenbergite, limonite.
5. Augite (15 to 20 per cent. of iron oxides), pleonaste, arfvedsonite.
6. Hornblende, augite (poor in iron), epidote, pyrope.
7. Tourmaline, bronzite, idocrase.
8. Staurolite, actinolite.
9. Olivine, pyrite, vivianite.
10. Biotite, chlorite, rutile.
11. Haüyne, diopside, muscovite.
12. Nepheline, leucite, dolomite.

It has been already mentioned that, owing to variations in composition exhibited by many minerals (especially in point of iron percentage), such lists ought not to be regarded as being accurate.

Perhaps the most noteworthy feature of Doelter's work with the electromagnet, was that of his experiments on crushed rocks. He attempted the separation of the mineral constituents as far as possible by the electromagnet alone, and stated the results quantitatively. But the fact that he operated on the dry crushings detracts seriously from the merit of the results he obtained. The character and extent of his separations may be seen from the following instances compiled from his results.

Nepheline Syenite, Antao Island

Magnetite	5 per cent.
Augite and hornblende	30 „
Nepheline and felspar	65 „

Phonolite of Praya

Magnetite	4 per cent.
Augite	11 „
Felspar and nepheline	85 „

Compact Basalt, Santiago Island

Magnetite	9 per cent.
Augite	39—46 „
Olivine	6—10 „
Plagioclase	32—44 „

Of the above results, we may take that for the nepheline syenite as possibly accurate. In the cases of the phonolite and basalt, however, we may reasonably inquire what has become of the undifferentiated ground of the rock. Indeed, it is fairly obvious that accurate results cannot be got by physical methods when dealing with hemicrystalline or very

compact types of rocks. The method can only be trusted quantitatively when applied to holocrystalline rocks, in which the particles obtained by crushing consist of individual (*i.e.* unmixed) minerals. In fairness to Doelter, however, it should be admitted that he was aware of the fact that in the case of hemicrystalline rocks the results were somewhat unsatisfactory. But in his enthusiasm for the method he went so far as to claim even for these, that they were of value as controlling and supplementing the results of chemical analysis. This claim may be fully respected when applied to holocrystalline rocks, but its assertion in the case of hemicrystallines is by no means warrantable.

The conclusions to which Doelter was led by the results of his experiments with the electromagnet summarise in an admirable way the scope of that instrument's utility as applied to rocks. His conclusions were: (1) that the electromagnet is of great service in petrographical studies; (2) that minerals can often be isolated by its aid which cannot be conveniently isolated by any other means; (3) that it is especially useful when applied in conjunction with the use of heavy liquids; (4) that the separations made by it, even when incomplete, are generally of great use, while in some cases they may be taken as being of somewhat definite quantitative value.

In a criticism of Doelter's work, Pebal[1] called attention to the fact that, when operating on fine crushings, the separation can be made more efficient by keeping the crushed fragments immersed in water during the process. Doelter attempted to refute this recommendation made by Pebal; but a comparison of experimental results indicates that the recommendation is a very good one, and that its adoption substantially increases the accuracy of the results for the finer crushings.

Mann[2] used the electromagnet to isolate augite for analysis from certain phonolites. He followed Pebal in the use of the wet method of separation, and denounced the dry method of Fouqué and Doelter. Mann also adopted a novel procedure in making some of his separations. He placed his magnet horizontally, and allowed the mineral fragments to fall in water

[1] *Sitzungberichte*, Wien, 1882, Band lxxxv. Abteilung i.

[2] "Untersuchungen über die chemische Zusammensetzung einiger Augit aus Phonolithen und verwandten Gesteinen," *Neues Jahrbuch für Mineralogie*, etc., 1884, Band ii.

through a glass tube, which was placed vertically between the poles of the magnet. The tips of the poles were only 5 mm. apart, and were chisel-edged, so as to concentrate the lines of force. Mann had little or no confidence in the use of the electromagnet quantitatively. He made numerous attempts to estimate the amount of augite in his phonolites by this method, doubtless encouraged by Doelter's example, but his results showed so much variation that he abandoned them as untrustworthy. As already pointed out, however, such rocks can scarcely be expected to yield even approximately accurate quantitative results.

It is beyond the scope of this article to deal with the many and elaborate inventions made during the last twenty years or so, by Wetherill and others, in applying the electromagnet on a large scale to ore-dressing operations. Those requiring information on this matter may be referred to the book by M. Korda already quoted (published by L'Éclairage Électrique, 40, Rue des Écoles, Paris), and also to the descriptions given by Richards,[1] Langguth,[2] and Witter.[3]

From the foregoing review of work done on the subject of the magnetic method of mineral separation, it is clear that the possibilities of the method have been somewhat fully considered by the various workers who have used it. In spite of this fact, however, any one wishing to use the electromagnet in petrographical work would find some difficulty in getting helpful guidance as to the best mode of procedure. To such, the following practical hints, tested in the course of some experience with the electromagnet, may be found useful.

3. The Apparatus Required

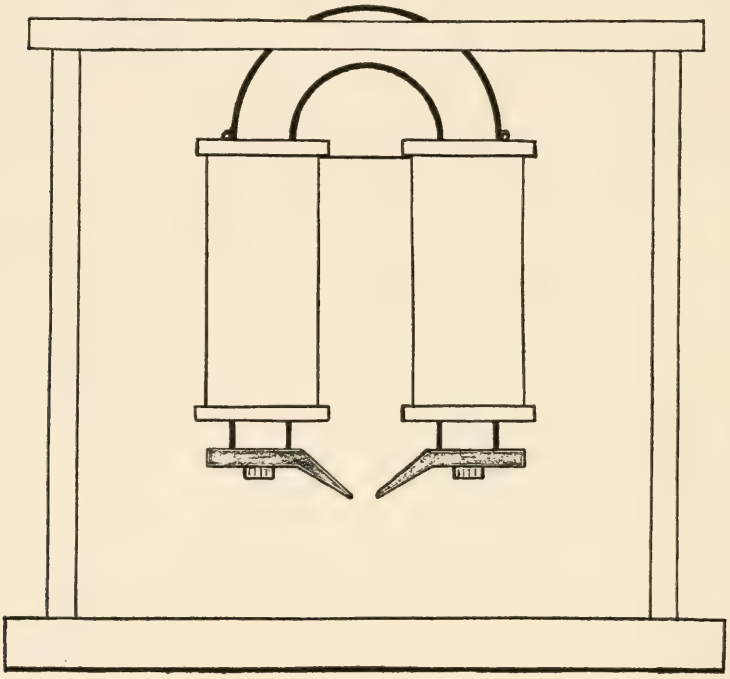
If expense can be disregarded, a magnetic separator of the Wetherill pattern is well worth having, especially when experiments are to be done on a large scale. A good example of the use of such a separator in this way is provided by a recent investigation as to the commercial value of certain heavy placer

[1] *Ore Dressing*, vol. ii. 1903. Published by *The Engineering and Mining Journal*.

[2] "Die Entwicklung der magnetischen Aufbereitung," *Zeitschrift f. Electrochemie*, Band vi. 1899.

[3] *Zeitschrift f. Angewandte Chemie*, 1899.

sands in the United States.[1] Such an instrument, however, is a decided luxury, and goes far beyond the needs of the average laboratory investigation. For ordinary purposes it suffices to use a magnet such as that illustrated by the accompanying figure. This electromagnet is one of the ordinary pattern, and is supported on a wooden frame. It consists of a cylindrical piece of soft iron, 1 in. in diameter, bent into U-shape, and having vertical limbs about 6 in. long and 3 in. apart. Each limb



is provided with a bobbin, on which is wound seven layers of insulated wire (16-gauge), each layer having about forty turns. Two pole pieces, consisting of soft iron about $1\frac{1}{4}$ in. wide and $\frac{1}{3}$ in. thick, are slotted so as to move over screw clamps which fit into the ends of the limbs. By this means the pole pieces can be adjusted in any desired position. As already pointed out, this was the device adopted by Faraday to secure a magnetic field of strong but variable intensity.

[1] *Investigation of Black Sands from Placer Mines*, by Day and Richards. Bulletin No. 285, p. 150, United States Geological Survey, 1906.

The adjacent portions of the pole pieces should be bent downwards, but not at right angles, narrowing slightly and thinning towards the tips, somewhat after the manner suggested by Doelter. The practice of having the adjacent ends of the pole pieces bent downwards at right angles in the way recommended by Rosenbusch[1] is very faulty. It is clear that with such an arrangement the lines of force must be distributed over all the space between the vertical plates, and as only the tips are used, most of the magnetic force is thereby wasted.

The magnet may be conveniently put into action by an eight-volt secondary battery of the portable Lithanode type. It is an additional convenience if, as is usually the case, the battery be arranged so that two, four, six, or eight volts can be obtained, as this affords an additional means of varying the intensity of the magnetic field.

Instead of a secondary battery an ordinary current, such as is used for lighting purposes, may be used, in combination with some form of resistance apparatus. A dynamo or a Bunsen battery may also be used as a substitute.

The wire connecting the battery with the electromagnet should be provided with a simple lever-switch arrangement, by which the current can be switched on or off as required.

The simple apparatus thus outlined will do all that is necessary in the way of isolation and separation, with such small amounts as one usually uses in the examination of sands and rocks generally.[2]

It may be cheaper, but not so convenient, to use a compound and permanent horseshoe magnet, as suggested by Delesse. Moreover, such a permanent magnet may be provided with adjustable pole pieces, like those already described for the electromagnet. But, in the absence of some mechanical device for suspending the action of the magnet on the grains, and thus permitting them to fall, such an arrangement is scarcely suitable for making separations.

[1] See *Mikroskopische Physiographie der petrographisch wichtigen Mineralien*, vol. i. part i. p. 431, 1904.

[2] This apparatus, including an eight-volt secondary battery, an electromagnet, and a switch, is supplied for the modest sum of about £3 10*s*. by the General Electric Co., 71, Queen Victoria Street, E.C. The electromagnet alone costs about £1 10*s*.

4. Preparation of Material

In the case of sands, the separation can usually be made without crushing, as the grains are generally small and of a simple character; but it is often convenient to sift, in order, as far as it is practicable, to secure uniformity of size among the grains.

With rocks, the degree of crushing required depends upon the texture, but as a rule the diameter of the grains obtained should not exceed 0·25 mm. The crushing should be done so as to secure a minimum of powder, especially in quantitative operations. This is effected by sifting at frequent intervals during the crushing process. The powder should be washed off, and, if necessary, treated separately in the wet way according to Pebal's suggestion. In any case the treatment of the powder usually gives unsatisfactory results, although for quantitative purposes it obviously cannot be neglected. On this point it is important to note that some minerals powder more readily than others, hence the proportion of any mineral present in the powdered portion will differ from that of the same mineral in the coarser portion of the crushings.

For the purposes of isolation, or in merely qualitative separation, the powder may be washed off and rejected after a cursory examination with the microscope.

5. Separation of the Minerals

Magnetite, if present, should first be extracted by a weak permanent magnet—an operation which is facilitated by covering the poles with a movable paper cap. The portion thus extracted should be carefully examined, as it may contain pyrrhotite and even hæmatite, both of which are very strongly magnetic. Ilmenite is not extracted by a weak magnet, except in the finest powder, and then only to a small extent.

The remainder of the grains are placed on cardboard, and, assuming the current to be switched on, are presented to the poles of the electromagnet. The cardboard is then removed, the current shut off, and the adhering grains allowed to drop into a cardboard box placed under the poles. This is continued till no more grains adhere to the poles. A certain amount of non-

magnetic and less magnetic material is, as a rule, mechanically enclosed in the most magnetic portion of the first separation. Hence the operation should be repeated till no residue remains behind, or till the separation is satisfactorily made. In the presence of fine powder it is practically impossible to get a good separation in the dry way, due to the fact that non-magnetic grains are mechanically enclosed in a mesh of magnetic grains—a defect which seems to be largely eliminated by having the grains immersed in water during the separation.

The actual details of the separation will depend upon the character of the specimen, and must be left to the judgment of the operator. A little experience suffices to indicate the best course to adopt in any given case. If a number of minerals of suitably varying permeability be present, the most permeable are first of all separated in a comparatively weak field, after which the field is intensified to secure the separation of a less magnetic ingredient.

The manner in which the grains are presented to the poles depends upon whether they are strongly or weakly attracted. In the former case the grains should not be permitted to touch the poles, while in the latter case the poles and the grains should be brought into contact. Thus, if the poles be inserted in a mixture of ilmenite and garnet grains, with a field of medium intensity, both minerals are extracted. But if the grains be not allowed to touch the poles, it will be found that, at a certain distance, the ilmenite is withdrawn and the garnet left behind. Further, by this means less non-magnetic material is enclosed with the ilmenite than is the case when the poles are inserted among the grains. On the other hand, in the case of a mixture of monazite, zircon, and quartz, the poles may be inserted among the grains, in order to extract the monazite, which is only slightly magnetic.

It is, of course, not possible by the magnetic method to separate minerals which agree or differ only slightly in permeability. For instance, hornblende cannot be separated from augite of similar composition; garnet and rhombic pyroxene are commonly inseparable; and some chromite cannot be separated from garnet.

As an example of separation, we may cite the following. The specimen was a concentrate obtained by washing a river sand. The minerals present were ilmenite, magnetite, garnet,

zircon, rutile, monazite, sillimanite, and quartz. The result of the magnetic separation was as follows:

	Per cent.	
Magnetite	about	1·3.
Ilmenite, Garnet	„	70·5 (only a trace of garnet).
Monazite	„	5·6.
Rutile, Zircon, Sillimanite, Quartz	„	22·5 (chiefly zircon).

In this case the monazite was almost completely isolated from the other ingredients, and the chief object of the separation was to determine its amount quantitatively, so as to get an approximate estimate for the amount of thoria in the total concentrate. In such an instance, when once the amount of thoria peculiar to the monazite grains of a district has been determined by chemical analysis, it becomes an easy matter to estimate the approximate thoria percentage of a concentrate by magnetic separation alone. Such estimates usually agree fairly closely with the results of chemical analysis.

Even in the absence of exact quantitative results for each mineral, the separation of the sand into groups of constituents gives a very clear idea of its mineral composition, and greatly facilitates examination with the microscope.

Another example of the usefulness of the electromagnet, especially when used in conjunction with other methods, may be taken from its application to a crushed rock. It is an especially useful means of isolating, or observing the presence of, certain accessory minerals in small quantities, such as apatite, rutile, zircon, and pyrite. The rock in question was an olivine gabbro; it was partially ophitic and medium-grained in texture. Twenty grams of the crushings were treated with the hand magnet to extract the magnetite. The remainder was treated with the electromagnet in a fairly strong field and divided into two parts: the magnetic portion was found, on examination with the microscope, to consist of a mixture of pyroxene (partly rhombic), olivine, hornblende, and brown biotite; the non-magnetic portion consisted almost entirely of plagioclase, with a little apatite and zircon, together with traces of pyrite and quartz. The separation

was somewhat imperfect, and the following result can only be regarded as approximately correct:

	per cent.		per cent.
Magnetite (titaniferous)	2·9	Plagioclases	
Pyroxene		Apatite	
Brown biotite		Zircon	
Green hornblende	43·0	Pyrite, Quartz	traces 54·0
Olivine			

The non-magnetic group, which, as already stated, consisted almost entirely of plagioclases, was then treated with heavy liquids. In this way the plagioclases and apatite were each isolated. From the zircon and pyrite thus remaining, the zircon was isolated by heating till the pyrite was partly oxidised, after which it was separated magnetically. The zircon thus isolated consisted of crystals of the ordinary type, colourless, and having the characteristic inclusions. In amount they were almost too small to be weighable, forming less than 0·01 per cent. of the rock, and yet they proved to be substantial objects for microscopical study.

Some idea of the effectiveness of this method of dealing with small quantities of zircon may be gathered from the following considerations. The largest zircon crystal obtained had dimensions about 0·5 × 0·1 × 0·1 mm. Ten such crystals weigh less than 0·25 mg., though they can be handled with ease for microscopical purposes. Such an amount of zircon obtained from 20 grams of the rock would amount to about 0·001 per cent.

The above process for determining the presence of small quantities of zircon is to be recommended, as it is a simple one and takes little time. Moreover, zircon in such small quantities appears to be frequently present even in the most basic rocks, such as olivine gabbros and basalts, and it is then practically impossible even to detect its presence by chemical methods. Further, it would appear that zircon in such small quantities generally eludes observation in thin sections, judging from the rarity of the cases in which it is mentioned in descriptions of basic igneous rocks. It should be recalled that Chrustschoff, partly by elutriation, and partly by treatment with acids, isolated small quantities of colourless zircon from many varieties of rocks. One of the rocks he examined was a basalt,

from 300 grams of which he obtained 0·022 gram of zircon—*i.e.* about 0·007 per cent. The method used by Chrustschoff,[1] however, lacks the neatness and precision which is attainable by the use of the electromagnet in combination with the use of heavy liquids.

6. Conclusion

To enter at further length on a description of the magnetic treatment of rock-forming minerals would unduly prolong this article. Sufficient has been stated to indicate that, to students of petrography, the electromagnet is an instrument of considerable value. It only remains to point out that, like every other means of observation, its sphere of usefulness is a limited one, and too much should not be expected from it. The presence of magnetic impurities in otherwise non-magnetic minerals is obviously a disturbing factor of great importance. For this reason, the use of the magnet should in all cases be controlled by examination with the microscope, and no separation should be taken as being exact, without confirming the purity of the separated portions in this way. Used in this manner, the method of magnetic separation is one which gives great assistance as a mode of physical rock analysis. Those who are anxious to make themselves in some measure independent of rock sections, and to avail themselves of the many advantages offered by a systematic study of crushed rocks, will find it a most useful adjunct in a somewhat neglected field of work.

[1] "Beitrag zur Kentniss der Zirkone in Gesteinen," *Tschermak's Mittheilungen*, Band vii. 1886.

THE COAGULATION OF THE BLOOD

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1. Introductory

In all vertebrate and invertebrate animals which possess either a true vascular or a pseudo-hæmal system, it is known that the liquid within these channels is in a state of continual or intermittent movement during life. In order that this condition shall be maintained, the blood or lymph or tissue-fluids contained within both the lymphatic and blood-vascular system must possess only a small degree of viscidity, which, apart from the suspended morphological bodies, depends upon their content in protein substances. The actual viscidity of blood varies scarcely at all during life, though its viscosity appears to vary within limits and to be largely dependent upon the corpuscular richness; an excessive number of corpuscles in the unit volume increases the friction-coefficient of the blood, thereby throwing extra work upon the heart. Blood which escapes from the blood-vessels into the extra-vascular regions of the body may or may not exhibit that change in viscidity which all

physiologists have recognised to be, next to the colour, its most distinctive feature outside the body. A gradual change in consistence takes place from the moment blood is shed, until, as a firm jelly, it forms a clot which is a cast of the vessel containing it. The plasma or fluid in which during life the red corpuscles and leucocytes floated has thus formed a single coherent mass of fibrin and corpuscles. This forthwith commences to shrink, with the consequent production of a spontaneously non-coagulable liquid or blood-serum.

In 1891 Lister[1] drew attention to the fact that, although blood may clot, no marked retraction of the clot due to a shrinking of the fibrin occurs when blood has been received in a vessel rendered sterile by heat or by washing it out with weak perchloride of mercury. A similar phenomenon is frequently seen when blood is collected for obtaining antitoxic sera. Hayem[2] and his pupils have also observed the absence of serum from the clotted blood of patients with pernicious anæmia or purpura hæmorrhagica. They attach a special importance to this non-retraction of the clot for the positive diagnosis of pernicious anæmia and most forms of purpura hæmorrhagica, and consider the phenomenon is of even greater value than a histological examination for the recognition of the former disease. This non-retraction of the clot is at present unexplained, but since it is a feature of clotted plasma in contrast to normal clotted blood, it is probably dependent in some way upon influences exerted on the fibrin by the imprisoned corpuscles or, according to Hayem, the blood-platelets, since the plasma of birds, which may contain only a few or no corpuscles, will, on being caused to clot by the addition of tissue-extract, show no subsequent retraction of the clot—a fact which has been noticed by Delezenne,[3] Fuld,[4] and Spangaro.[5] The fibrin, which forms but a very small amount of the bulk of the clot, subsequently alters in its physical characters, becoming more soluble. The extent of fibrinolysis and the rate at which this occurs differs in different animals; it is also a subject of much interest, since a study of the conditions under which it occurs

[1] *Lancet*, p. 1082, 1891.
[2] *La Semaine médicale*, November 1896; *Comptes rend.* January 1901.
[3] *Arch. de Physiol.* p. 333, 1897.
[4] *Hofmeister's Beiträge*, ii. p. 514, 1903.
[5] *Arch. ital. de Biologie*, xxxii. p. 210, 1900.

may conceivably be of direct value in bringing about the disappearance of intra-vascular blood-clots, such as are common in disease. The observations of Dastre,[1] who attributes fibrinolysis to the action of a fibrinolytic enzyme, accord best with the ascertained facts. Arthus and Huber[2] also confirm his statement that bacteria are not essentially concerned in the process. In experimental phosphorus poisoning not only may a firm clot rapidly pass into solution in the serum, but, as Jakoby[3] has shown, the serum in these cases possesses an intense fibrinolytic action on normal blood-clot.

Among the cardinal facts concerning blood when this liquid is considered as a whole, the knowledge that the blood on escaping from the body coagulates must be far more widely spread than are some other points of equal interest, such as the possession by the organism of a large excess of blood beyond the amount which is actually required for the performance of its functions, and that when the body-cells die or are diseased, as well as in a variety of conditions such as deprivation of food or on the introduction of foreign material into the circulation, the individual strives by every means in its power to maintain the constituents of the blood at their normal, absolute, and relative values. That the phenomenon of coagulation is a protective one is sufficiently obvious. When blood coagulates on the surface of or outside the body it is a normal process, just as clotting within the vessels is pathological. Cells detached from an organism may show instantaneous chemical and physical changes which are variously interpreted as signs of commencing death or signs of continuing life. In connection with this, recent papers by Vernon[4] and Schryver[5] may be consulted; and the latter has shown that, at any rate in the case of intestinal epithelial cells, disintegrative processes commence immediately these are detached from the body. But from a morphological point of view no cell or part of a cell detached from an organism exhibits such a rapid change as that shown by dying blood, and the rapidity of this change or rate of coagulation varies in different animals, and in the same animal under different

[1] *Comptes rend.* xlv. p. 995; *Arch. de Phys.* xxv. p. 661, 1894.
[2] *Arch. de Physiol.* xxviii. p. 857, 1896.
[3] *Zeitschrift f. phys. Chem.* xxx. p. 174, 1900.
[4] *Journ. of Phys.* xxxv. p. 53, 1906; *Zeits. f. allg. Phys.* vi. 1906.
[5] *Biochem. Journal*, vol. i. No. 3, 1906.

physiological conditions. In man it has been found that blood when shed either does not necessarily coagulate, as in hæmophilia, or does so slowly or rapidly. We must admit that the appearance of fibrin in shed blood is definite evidence of its altered state. This may take place within 10 to 20 seconds from the time blood is shed from a wound, for when examined as a stretched film at the temperature of the body in a moist chamber, a thread of fibrin some millimetres in length can be lifted from the film. In this interval of time, therefore, a gross change occurs—the appearance of fibrin, which does not exist in blood; and it is permissible to suggest that possibly blood commences to undergo other changes less easy to recognise *immediately* it leaves the body.

2. The Coagulation Rate of Human Blood

A knowledge of the rate of coagulation of human blood is considered by many clinical observers to be of diagnostic importance. It is difficult, if not impossible, to accurately ascertain this rate, since the results of different observers are conflicting, and this is due partly to the diversity in the methods employed as well as to the inherent difficulties in carrying out a series of successive experiments under exactly similar conditions. In this country most of the data have been obtained by the methods suggested by Sir Almroth Wright. The figures of this observer for normal human blood at a temperature of 20° C. are about 4 min. 50 sec. A series of between 300 and 400 observations made by this method at a temperature of 19·4° showed that in healthy women the average time was 7·75 min.,[1] though it may be as short as 5 or as long as 10 minutes. The average value obtained for normal men by an entirely different method at 20° is given at 7·8 min.[2] My own figures, given by another method but taken at the same temperature, average 8 min. 45 sec. Bürker[3] has devised yet a fourth method, and his recent figures show that the rate varies between 6 and 7·5 min. at 20°, although in the same individual, according to the time of day, amount of exercise, or kind of food, the rate of

[1] Douglas, *Brit. Med. Journ.* March 26, 1904.
[2] Brodie and Russell, *Journ. of Phys.* p. 403, 1897.
[3] *Pflüger's Arch.* cii. 1904.

coagulation may be as low as 5 minutes or as high as 14·5, a statement which I can confirm, though the method which was employed differed from that which he has described.[1]

3. State of the Subject at the Close of the Year 1880

The examination of the blood was essentially a study of those few early observers whose work at that time comprised not only the practice of medicine, but also all those subsidiary sciences bearing upon this subject which are to-day in some cases unfortunately so widely dissociated from medicine. During this time, which was succeeded by the period of humoral pathology, the contributions of Hewson and John Hunter form a definite starting-point in our knowledge of the coagulation process. The early discoveries of Hewson, those of Buchanan of Glasgow in 1845, those of Denis, who isolated a sero-fibrin, which he subsequently termed plasmine, from salted plasma—a substance which he proved, when mixed with water, gave a clot—down to the earlier work of Alexander Schmidt and Olaf Hammarsten on the conditions and factors influencing coagulation, have been already admirably described[2]; and our definite knowledge concerning the process of coagulation of the blood outside the body at the close of the year 1880 may, in the light of subsequent work, be briefly stated. Blood retained within the living vessels does not clot readily. Further, the plasma of blood clots in the same way and as readily as the whole mass of the blood. Contact with foreign material accelerates the clotting process or conceivably induces this, since blood remains unclotted for days when removed from the body with its containing vessel, or even if the wall of the vessel be replaced by a perfectly clean glass tube (Lister[3]). A definite protein substance—fibrinogen—can be precipitated from plasma, and solutions of this can yield fibrin. Moreover, fibrinogen exists as such in the plasma of normal living blood, since it can be thrown down as an insoluble body from living blood. The important proof of this fundamental statement is due to Fredrique, who, in 1877, repeated an old experiment of Hewson. He removed the jugular vein of a

[1] Buckmaster, *Morphology of Normal and Pathological Blood*, p. 212, 1906.
[2] Gamge, *Text-book of Physiological Chemistry*, vol. i. 1880.
[3] *Ibid* vol. i. p. 79.

horse, together with the contained blood, by ligaturing the vessel in two places. The operation was carried out aseptically, with a minimum amount of damage. The corpuscles settled down, and from the uncoagulated plasma an insoluble fibrinogen separated out at 56° C. A substance varying in activity, which is destroyed by heat, can be obtained from coagulating or coagulated blood. This is thrombin, or fibrin-ferment (Alexander Schmidt, 1872), which does not exist in circulating blood, and therefore coagulation does not occur during life; but thrombin appears when blood dies, and the surplus which is not used is found subsequently in the serum. The ferment is destroyed by boiling. It cannot be obtained as a pure product. We recognise the substance, as is the case with all ferments, by its specific action, that of converting a soluble fibrinogen into an insoluble fibrin. Under the microscope certain changes can be witnessed in a film of shed blood. From isolated highly refracting bodies, the blood-platelets, or from groups of these, strands of less refractive material can be seen to extend, form a network, entangle both the red and white corpuscles, and form a clot (Mrs. E. Hart, 1879[1]).

These statements embody the main facts known in 1880, and, though they may be found in all text-books of physiology, it is convenient to mention them here, since the workers of the past twenty-five years have been compelled to take these certain facts into account, and, indeed, no theory of coagulation can ignore them. Theories are not necessarily explanations, and the successive output of work in connection with coagulation has tended to the creation of a somewhat mystifying terminology and to the construction of innumerable theories. Apart from original papers, special contributions in English,[2] French,[3] and German volumes,[4] together with the admirable article by Morawitz,[5] have rendered it possible to sift out the less definite from those more definite facts which have thrown light on the nature of the coagulation process both within and outside the body.

The work of Alexander Schmidt himself, apart from that

[1] *Quart. Journ. of Microscopic Science*, xxii. 1882.
[2] E. A. Schäfer, *Text-book of Physiology*, vol. i. p. 168, 1898.
[3] Arthus, *La Coag. du Sang:* Paris, 1899.
[4] E. Schwalbe, *Untersuch. über Blutgerinnung*, 1890.
[5] *Ergebnisse der Physiol.* p. 307, 1905.

of his pupils of the Dorpat school, on the question of coagulation extended from 1860 to 1895. His conceptions as to the nature of the process underwent modification rather than destruction by other observers. Hammarsten in particular showed:

1. That all natural and artificial fluids containing fibrinogen can be caused to coagulate with fibrin-ferment.

2. That no other protein constituent of blood-plasma can be considered to exert any specific action in the process of coagulation, and that where such an action is apparent it is due to contamination of the substance with thrombin or fibrin-ferment, since the repeated purification of any protein which apparently induces a formation of fibrin abolishes this action, just as a temperature of 56° to 69° destroys any ferment adhering to the substance, though the substance itself is not apparently physically altered.

3. Fibrin-ferment converts fibrinogen into fibrin, a change which does not occur in living blood, since the ferment appears only in shed blood. In this phase of the coagulation process fibrinogen passes through a stage of soluble into insoluble fibrin, exactly as caseinogen passes into a soluble and then into an insoluble casein—though, as will be seen subsequently, the coagulation of fibrinogen-containing fluids by thrombin is in no sense paralleled by the action of rennin on caseinogen, as Arthus and Pagès originally believed.

4. Phases of the Coagulation Process

Since coagulation depends on the conversion of fibrinogen into fibrin in a series of steps by a ferment body which is non-existent during life, the phases of coagulation must be:

1. Formation of thrombin.

2. Conversion of fibrinogen into fibrin where a stage of soluble fibrin precedes the insoluble stage.

The grounds for this conception of the second phase—a belief that before any separation of fibrin occurs the fibrinogen suffers change—depend on some remarkable observations made by Hammarsten.[1] Although fibrinogen in hydrocele fluid[2] co-

[1] Quoted from *Jahresb. f. Tierchemie*, 1876.

[2] The spontaneously non-coagulable exudation found in a pouch derived from the peritoneum, which envelops the testis.

agulates at 60°, and an apparently identical fibrinogen in blood-plasma at 56°, the addition of fibrin-ferment to hydrocele fluid at once reduces the coagulation-temperature of this globulin to 56°. Ferment-free hydrocele fluid remains clear when thawed after freezing, whereas it appears turbid if treated in the same way after the addition of ferment. Since the same phenomena are seen when solutions of fibrinogen are employed instead of blood-plasma, it would appear that in the process of coagulation all the fibrinogen does not become fibrin, but a part of this, fibrin-globulin, which is a soluble protein coagulating at 64°, separates out. It is conceivable that, under the influence of thrombin, fibrinogen suffers a hydrolytic change into two bodies. Hammarsten believed that the fibrin-globulin was a remnant of the soluble fibrin, since the relative amounts of fibrin and fibrin-globulin produced by ferment action vary so enormously that a simple hydrolytic process is impossible. Recently Heubner[1] has stated that never more than half the fibrinogen in a liquid becomes fibrin, and inclines to the view that a hydrolytic action is exerted by the ferment. Huiskamp[2] has prepared solutions of fibrinogen by precipitation with sodium fluoride, and found that these, neither by heat nor by coagulation with ferment, yield any fibrin-globulin. This product, therefore, is not produced when blood coagulates, but is either pre-existent as such in plasma, or, as a separate body, may be loosely attached to fibrinogen.

The greater part of the work on the coagulation question since 1880 centres around the first phase of the process—the formation of fibrin-ferment, but it would appear to be of little use in this place to discuss the theories of those whose real work will be remembered for the establishment of incontrovertible facts.

5. The Rôle of Calcium Salts in the Process of Coagulation

Hammarsten, in 1875, had already recognised that the addition of calcium chloride to solutions of fibrinogen increased the yield of fibrin which could be obtained on coagulation; but it was essentially a discovery of Reynolds Green,[3] fifteen years later, that calcium salts are absolutely necessary in order

[1] *Archiv f. exp. Path. u. Pharmak.* xlix. p. 229, 1902.
[2] *Zeits. f. physiol. Chemie*, xliv. p. 182, 1904.
[3] *Journal of Physiol.* 1887.

that coagulation shall occur in salted plasma. When these are removed by dialysis, coagulation never occurs. He further proved that calcium does not act like a ferment, since it is incapable of coagulating either the fibrinogen in a hydrocele fluid or solutions of this globulin. Salts of strontium in a less degree act like salts of calcium.

Arthus and Pagès[1] decalcified blood by the addition of 1 gramme of potassium oxalate to a litre of dog's blood or by 1·5 to 3 grammes of sodium fluoride (Arthus[2]), or by a strong solution of alkaline soaps. The oxalated plasma clotted simply on the readdition of calcium chloride. Arthus and Pagès believed that oxalated plasma contained thrombin, since it could coagulate fibrinogen solutions; and since, together with other experiments, it was shown that the yield of fibrin was characteristically raised or lowered by the calcium content of the plasma, they concluded that calcium played a definite part in the second phase of coagulation, and that fibrin was really a calcium compound of fibrinogen. Pekelharing[3] repeated and extended this work, and showed that although oxalate-plasma does not contain thrombin, it does undoubtedly contain a zymogen or prothrombin, which on being activated by calcium becomes an enzyme—in fact, is thrombin. The zymogen of a salt-plasma can be thrown down together with the globulins, and such a precipitate contains thrombin, while a similar precipitate thrown down from oxalate plasma has no ferment power, but acquires this on the addition of calcium chloride. Therefore the zymogen termed prothrombin becomes thrombin on the addition of calcium, and when once at this stage its activity can be shown to be no longer destroyed by the subsequent addition of an oxalate. Arthus and Pagès considered that calcium essentially played its part in the second phase of coagulation; while Pekelharing demonstrated that during the first phase, when a formation of thrombin takes place, this was effected by salts of lime. In this way the ferment was fully formed from its zymogen stage. In the second phase of coagulation Pekelharing considered that the ferment handed on the lime, so that it was associated with fibrinogen, and thus yielded a calcium compound

[1] *Arch. de Physiologie*, xxii. p. 739, 1890.

[2] *Journ. de Phys.* 1901.

[3] *Intern. Beiträge f. Virchow's Festschrift*, 1891; *Deutsche med. Wochenschrift*, p. 1133, 1892.

of this globulin which was known as fibrin. In the theory of Lilienfeld,[1] though the existence of thrombin is accepted, the idea that it plays any important part in the process of coagulation is denied, and the behaviour of calcium in the process is regarded as identical with the views suggested by Arthus, for whom fibrin was a calcium compound of fibrinogen or a thrombosin curd. Alexander Schmidt, however, denied the specific action of calcium for either phase of the coagulation process; its presence in a coagulable fluid only favours the conversion of a zymogen into an enzyme and the formation of fibrin from fibrinogen. He therefore included calcium salts with these substances, which, like strontium, and possibly barium, exert a directly favouring influence on the rate and extent of the coagulation process.

These conflicting views have been completely explained by Hammarsten,[2] whose researches were directed towards affording a sufficient answer to two questions:

1. Are salts of lime absolutely necessary in order that fibrin-ferment shall act upon fibrinogen?

2. Can the whole coagulation process in its two phases occur in the absence of calcium salts?

Hammarsten showed that the total calcium content of blood is in two states. That portion which is in solution can alone be precipitated by oxalate, while another portion, which is probably united in organic combination with the proteins of the plasma, cannot be detached. The non-coagulability of oxalated plasma is therefore a matter related to that fraction of the calcium which can be precipitated. When oxalate-plasma is cooled to 0°, Pekelharing had already shown that a granular precipitate gradually separates out; and in proportion as this occurs, so does oxalate-plasma lose its peculiar property of coagulating on the addition of calcium chloride. It was a logical deduction that this separated material was essential for coagulation, and from the supernatant oxalated plasma Hammarsten precipitated a calcium-free fibrinogen by lime-free sodium chloride, and found that a calcium-free fibrinogen could be caused to clot on the addition of a calcium-free solution of thrombin. By this experiment it was conclusively proved that the presence of calcium is quite unnecessary for the conversion of fibrinogen

[1] See *Text-book of Physiology*, ed. by Schäfer, vol. i. p. 172.

[2] *Zeitschrift f. physiol. Chemie*, xxii. p. 333, 1896, and *ibid.* xxviii. 1899.

into fibrin, and the latter body is certainly not a calcium compound of the former. A series of analyses confirmed this, since it was shown that the calcium content of fibrin is not higher than the fibrinogen which yielded it, and fibrin can be produced which contains only a trace of lime—0·007 to 0·0095 per cent. However, the absolute proof that calcium does take a specific part in the formation of fibrin-ferment, as Pekelharing believed, was confirmed by Hammarsten, since the material separated from cooled oxalated plasma contained a zymogen which could be directly and specifically activated by calcium salts, and induce coagulation of fibrinogen solutions, a property it did not possess unless these salts were added. Calcium salts or calcium ions, therefore, play an essential rôle in the first phase of the coagulation process by activating a zymogen. In this way thrombin, non-existent in living blood, originates in blood after it is shed. The absolute amount of calcium present is stated by Sabbatani[1] to be a negligible factor for the formation of thrombin. Only that portion which is in the ionic state is concerned in the process. The arguments for this view are that all physical methods which, like heat and cold, exalt or depress the amount of ionisation or affect the velocity of the ions, equally affect, accelerate, or retard the onset of coagulation. In the case of fluoride-plasma, which clots simply on the addition of water, the dilution may promote a sufficient degree of ionisation of the suspended lime salts.

6. Thrombin or Fibrin-Ferment

The interest attaching to this part of the question may be grouped around the three following facts:

1. The production of intra-vascular clotting by the injection of various tissue-extracts, and the development of a clot *in vitro* from non-coagulable or feebly coagulable liquids by the addition of tissue-extracts.

2. The discovery of Delezenne that the blood of those vertebrates which possess nucleated red corpuscles often does not spontaneously clot. Blood removed from birds such as the goose or pigeon with every aseptic precaution will yield a clear plasma which may actually commence to putrefy before it coagulates.

[1] *Arch. ital. de Biologie*, xxxix. 1, p. 333.

3. The recognition by Fuld and Spiro and by Morawitz that the term "thrombin" is applied to bodies which possess quite different properties.

Contrary to the results of previous observers in 1880, Edelberg,[1] a pupil of Schmidt, obtained intra-vascular clotting by the injection of solution of fibrin-ferment. In confirmation of the views of Schmidt that the fibrin-ferment was directly or indirectly a product of the leucocytes, Rauschenbach[2] in particular showed that not only leucocytes of the blood, but the cell-protoplasm of almost every tissue in the body, also yeast-cells (Wright), could markedly induce or accelerate coagulation in salted plasma, cooled plasma, and some, but not all, specimens of hydrocele and ascitic fluid. Tissues rich in nuclei possess this property not only *in vitro*, but when injected into the circulation—a fact which was definitely established by Foà and Pellacani,[3] who observed, moreover, that the tissue-extracts from the most varied sources, with the exception of the spleen, could induce intra-vascular clotting. Wooldridge[4] in particular confirmed these results, and in a remarkable paper showed that solutions of tissue-extract can not only cause a sudden death and produce extensive intra-vascular clotting, especially in the portal system, but that in dogs a definite dose per kilo body-weight can also produce conditions where the shed blood is found to be incoagulable. Further, a "Schutzimpfung auf chemischem Wege" could be demonstrated. This, the earliest example of an acquired immunity conferred by injection, was proved by showing that a small dose of injected tissue-extract, which Wooldridge subsequently termed B-fibrinogen, rendered a dog immune to a subsequent lethal dose of the same substance. These suggestive experiments, together with others on recognition of phosphorus in the extracts and his work on peptone-plasma led Wooldridge, like Rauschenbach, to speak of blood-plasma as protoplasma, and to hold that circulating blood contained within itself all that was essential for the coagulation process. The existence of fibrin-ferment played no part in his theory; both the coagulation and non-coagulation of blood was dependent upon the relations

[1] *Arch. f. exp. Path. u. Pharmak.* ii. p. 283, 1880.
[2] *Inaugural Dissert. Dorpat*, 1883.
[3] *Bir. clin. di Bologna*, p. 241, 1880.
[4] *Du Bois' Archiv*, 1881.

existing between the fibrinogen of blood and that other fibrinogen which originated from the tissues. He regarded the protoplasma as a living substance, capable, as he said, of being stimulated by such agents as carbon dioxide or weak acetic acid, so that a response or coagulation occurred.[1]

Tissue-extract is allowed by all observers to contain much nucleo-protein. The differences between this substance obtained from blood-plasma, leucocytes, or tissues such as the thymus or testis, and Schmidt's fibrin-ferment have been pointed out by many workers. Halliburton and Brodie,[2] among others, have insisted upon this difference. Whether nucleo-protein possesses a ferment action or whether in the preparation of this substance it becomes contaminated with thrombin, the same questions may be asked with reference to tissue-extracts, and investigations into the relations of these to the non-coagulating plasmata of birds have permitted a definite answer to be obtained, and at the same time enabled a large number of conflicting facts to be explained.

Although early observations on the coagulation of birds' blood showed that this quickly coagulated, Schmidt and Tiegel could not confirm this. The discoveries of Delezenne in 1897 that birds' plasma remained uncoagulated, that when the sedimented blood did coagulate the phenomenon started at the zone of leucocytes just above the red corpuscles and slowly extended upwards and downwards through the blood, and that both the blood and completely cell-free plasma quickly coagulated on the addition of tissue-juice from any source, have been confirmed by all observers. Among other work bearing on this subject that of Phisalix,[3] Fuld,[4] Fuld and Spiro,[5] Wright,[6] and Morawitz[7] may be mentioned here.

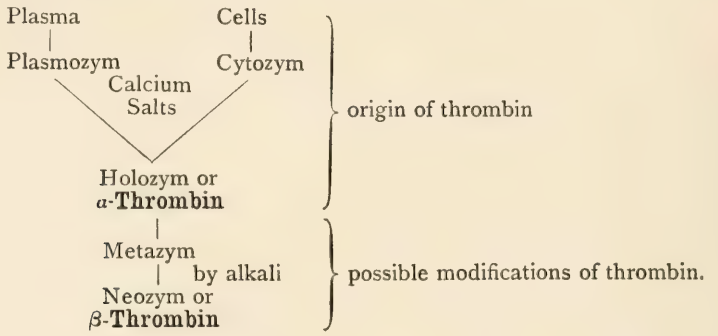
According to Fuld's view, whether thrombin action is similar or not to that of other enzymes, the formation of thrombin is due to the interaction of three factors which exist in the plasma of circulating blood or in plasma of unaltered blood outside the body. These are:

[1] Wooldridge, *Collected Papers*.
[2] *Journal of Physiology*, xvii. 1888.
[3] *Comptes rend.* li. pp. 881 and 885.
[4] *Centralbl. f. Physiologie*, p. 529, 1903.
[5] *Hofmeister's Beiträge*, v. p. 171, 1904.
[6] *Journ. of Phys.* xxviii.
[7] *Arch. f. Klin. Med.* lxxix.; *Hofmeister's Beiträge*, v. 1904.

1. Calcium salts.
2. A zymogen, or pro-ferment.
3. A substance which may originate from the corpuscles or from other tissues known as zymoplastic substance.

The pro-ferment which arises from the plasma is plasmozym; the substance originating from cells is termed cytozym. The interaction of these two and calcium ions yields a true thrombin or holozym. The subsequent destiny of this, when it is present in serum after the process of coagulation, is to pass into metazym, which is to be considered as a zymogen capable of passing into a ferment stage known as neozym, when it is activated by an alkali. The evidence for this conception, which may be expressed in the following scheme, can be better discussed with the help of later work, particularly that of Morawitz.

The formation and fate of thrombin would be indicated as follows (Fuld):



The cytozym of Fuld corresponds to the coagulating substance in tissue-extract; and since fowls succumbed in a few seconds to an intra-venous injection of cytozym, it was concluded that the formation of thrombin occurred in a circulating fluid which already contained calcium and plasmozym. The results of Arthus[1] obtained with fluoride-plasma are only in partial agreement with Fuld's observations. Non-coagulating fluoride-plasma is an excellent medium for ascertaining the existence of thrombin. Both blood-serum and Schmidt's thrombin produce coagulation in fluoride-plasma. This, however, remains non-coagulable when cytozym alone or calcium alone is added. It is a fair conclusion that tissue-extract therefore

[1] *Journal de Physiologie*, p. 887, 1901.

contains no thrombin, since it will not coagulate fluoride-plasma. However, a perfectly cell-free plasma from the bird, or peptone-plasma from the mammal, will clot perfectly with tissue-extract.

Blood allowed to flow about in the subcutaneous tissues coagulates much more readily than a control sample taken direct from the vessels,[1] and this, together with the observations already described, shows that, though tissue-extracts contain no thrombin, they do contain a substance termed by Morawitz thrombo-kinase, which is concerned in the production of thrombin.

Although Pekelharing and Delezenne believed that tissue-extract actually exerted its influence in virtue of its fibrin-ferment, Schmidt, Arthus, and Wooldridge denied this, and in a general way the action was attributed to the presence of nucleo-protein. In circulating blood this substance or zymogen is absent, but appears in shed blood. The prothrombin described by Schmidt he regarded as pre-existent and activated in the presence of lime salts by a zymoplastic substance, shed out of leucocytes. According to Schmidt, this is the substance found in tissue-extract.

In 1903 Morawitz proved that the zymogen or prothrombin of Schmidt and the zymogen described by Hammersten, Arthus, and Pekelharing are entirely different substances. They are both inactive stages of thrombin. One occurs in oxalate-plasma, and is activated by calcium salts and by nothing else. This is α-prothrombin, and is in part or entirely the material which separates out in cooled oxalate- or peptone-plasma. The other kind of zymogen, that of Schmidt, β-prothrombin, or Fuld's metazym, is peculiar to the serum separated from coagulated blood. It is non-existent in fluoride-plasma or in oxalate-plasma or in circulating blood. This form is not activated by calcium, but even in the absence of salts of this metal can be activated by weak acids or alkalies. The term metathrombin can be employed for this unactivated stage.

The development of thrombin from metathrombin is easily produced by weak alkali. When serum is exposed to the air for a few days, any thrombin present completely disappears, and the fluid possesses only metathrombin. In the following table these facts are made clearer:

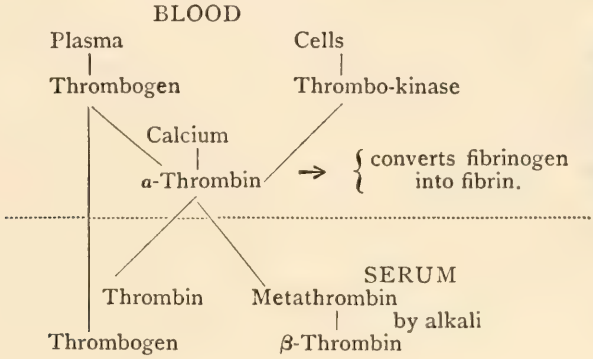
[1] Arthus, *Journ. de Physiologie*, iv. p. 281, and *Comptes rend.* liv. p. 136.

	Calcium.	α-Prothrombin, Zymogen	Thrombin	Metathrombin, Metazym, β-Prothrombin
Circulating blood . .	+	+	o	o
Oxalated plasma . .	o	+	o	o
Peptone-plasma . .	+	o	o	o
Fluoride-plasma . .	o	+	o	o
Serum from blood .	+	o	a little	+
Serum from any of the coagulated plasmata	+	o	a little	+

From the thymus, lymphatic glands, or the stromata of red corpuscles, a thermolabile substance can be extracted with a weak saline solution. This substance is, for the most part, thrombo-kinase, which soon becomes unstable in solution, though the extract, dried in a vacuum, yields a powder which only slowly changes. On fibrinogen solutions, even in the presence of lime, this extract produces no change; it is therefore not a thrombin such as occurs in serum. Exactly the same negative result follows when extracts from mammalian tissues are added either to solutions of fibrinogen or to oxalate- or fluoride-plasma, and it is immaterial whether the extracts are previously treated with calcium chloride or not.

On the other hand, the clotting of blood is accelerated, and the coagulation process in the plasma of birds, in peptone plasma, and sometimes in hirudin-plasma, forthwith commences on the addition of thrombo-kinase, provided calcium salts are present. The ferment-power of serum is also exalted by thrombo-kinase. From these facts Morawitz concludes that the development of thrombin results from the interaction of kinase with a body in coagulable liquids or in serum in the presence of calcium salts. This body is the substance recognised by Fuld as plasmozym, and may be termed thrombogen. This corresponds to *a*-prothrombin. Since *a*-prothrombin exists in fluoride-plasma as well as in all the non-coagulated but coagulable plasmata hitherto examined, the following conception of the coagulation process may be suggested. In the plasma of circulating blood a certain amount of fibrinogen, calcium, and thrombogen will be found. It does not coagulate, since thrombo-kinase is entirely absent, or if present in small amount is neutralised by anti-bodies in the blood. Solutions of thrombo-kinase or of substances capable of setting this free in the blood will forthwith give rise to thrombin, and be followed by intra-

vascular clotting. Outside the body the morphological constituents of the blood, and in particular the blood-platelets, yield kinase when these are brought in contact with non-living matter. The first phase of the coagulation process is thus initiated by the co-operation of thrombogen, calcium ions, and kinase.



The following table shows the accepted constituents of various plasmata on the suggested hypotheses of Morawitz, Fuld, and Spiro:

	Blood.	Serum.	Bird-plasma.	Oxalate-plasma.	Fluoride-plasma.	Peptone-plasma.
Thrombogen . .	+ ?	+	+	+	+	+
Kinase . . .	o	+ ?	o	+	+ ?	+
Thrombin . .	o	+	o	o	o	o
Metathrombin .	o	+	o	o	o	o
Calcium . .	+	+	+	o	o	+

Of the substances concerned in the production of thrombin, as described in the account just given, it would appear that very definite knowledge as to the sources or nature of thrombo-kinase and thrombogen in coagulable liquid does not exist. It is possible that kinase corresponds entirely or in part to the nucleo-proteid which apparently enters into the composition of the blood-platelets. Fluids such as goose-plasma, fluoride-plasma, or hirudin-plasma are devoid of kinase, while in oxalate or peptone-plasma this is present. On cooling these plasmata a granular precipitate occurs only in those which possess kinase, and this deposit is recognised in part to be nucleo-protein. As to the source or sources of thrombogen in blood there is

even more doubt. This body is not precipitated by cooling a liquid which contains it to 0° C., nor is it of a nucleo-protein nature. Suspensions of blood-platelets, obtained by centrifugalisation, have been regarded as yielding a supply of thrombogen. The prothrombin claimed by Schmidt to be present in circulating blood is apparently identical with thrombogen, and though this body is absent from plasma in cases of experimental phosphorus poisoning, the blood-platelets are present in large, if not excessive amount, and appear quite normal under the microscope. The repetition of old observations of Freund and Haycraft shows, moreover, that blood received in parafined or oiled tubes can be centrifugalised without clotting, and a perfectly cell-free plasma obtained, which clots on transference to a glass vessel.[1] But such a plasma contains no thrombin while in contact with paraffin, since the plasma can be decalcified. The contact-action of a foreign body therefore appears to be a deciding factor for the actual co-operation of those bodies which the researches of Morawitz have indicated as the probable factors in the formation of thrombin.

A large number of substances which possess toxic and ferment properties have been described as constituents of various snake-venoms. It is known that exceedingly minute amounts of the venoms of certain Australian and Indian snakes[2]—·0001 gramme per kilogramme body-weight—will cause intravascular clotting in dogs, cats, rabbits, and other animals. Such venoms contain veritable thrombins or fibrin ferments, which can clot blood *in vitro* (Lamb). They are destroyed in fifteen minutes by a temperature of 75° C. and impaired in power by filtration through a gelatine filter. Further, the ferment does not appear to be used up in the process of coagulation (C. J. Martin). That the clotting properties of venoms is dependent upon a formed thrombin appears certain. Their clotting power "is not due to their action upon prothrombins or thrombogens contained in plasma, as the presence of calcium ions is unnecessary." The venoms clot 10 per cent. oxalate plasma *in vitro* as rapidly as ·2 per cent., and their action is the same upon the following: citrate, fluoride and magnesium sulphate plasma, hydrocele fluid

[1] Bordet and Gengou, *Annal. de l'Inst. Pasteur*, 1903 and 1904.

[2] *Pseudechis porphyriacus*, *Notechis scutatus* (Australia); *Echis carinatus*, *Vipera Russellii* (India).

and solutions of fibrinogen prepared from blood plasma. The thrombins contained in venoms probably act as catalysts, and induce a formation of fibrin from fibrinogen. In this respect the behaviour of thrombo-kinase to birds' plasma, when coagulation is induced by the kinase effecting such a change in thrombogen in the presence of calcium that fibrin-ferment is formed, is in no way comparable to the action of venom on blood. For the thrombin of snake venom the rate of clotting varies with the amount of venom employed, so that the time multiplied by quantity of venom is constant.[1]

7. The Intra-vascular Injection of Peptone

From the fate which has overtaken nearly every theory which has been advanced to explain the coagulation process, it is permissible to predict that the one advanced by Morawitz will eventually prove to be only a provisional working hypothesis. If thrombo-kinase can be derived from any one or all of the morphological bodies in blood, it is difficult to understand why, during life, small quantities of this do not exist in circulating plasma. That the leucocytes at any rate disintegrate while circulating is almost certain. Contrasted with the duration of the life of the erythrocytes, the polymorphonuclear leucocytes survive only a few days. Any liberated kinase will play a part in the production of thrombin, and this will be rendered inactive by some anti-body or, what is improbable, since it is somewhat stable, changed into another form. It is also conceivable that any liberated kinase may be also neutralised, so that no formation of thrombin is possible.

The existence of thrombin cannot be demonstrated in many extra-vascular plasmas, though both proteolytic enzymes and anti-enzymes have been described in blood-serum and considered to be existent in plasma. Bordet and Gengou have shown that neutral salts hinder or suppress the formation of thrombin from its precursors, and in stronger concentration entirely abolish the activity of any thrombin which may be present. Similarly, the cooling of plasma acts essentially in the first manner. Arthus arranges the bodies which restrain coagulation into two groups :

1. Those substances—of which peptone, or rather deutero-

[1] C. J. Martin, *Journ. of Phys.* xv. 1894 ; xx. 1896 ; xxxii. 1905.

albumose, is the type—which exert specific action only when they are introduced into the circulating blood. The reaction of the organism, consequent upon intravenous injection, is essential, in order that substances restraining coagulation shall arise.

2. Substances which act independently and directly upon blood both inside and outside the organism.

Various animals react differently to peptone injection, and individuals of the same species require various amounts of peptone per kilogramme body-weight. To obtain blood which, when shed, shall be completely incoagulable, the injection must be made into the circulation with rapidity, and the animals should be fasting. Contejean states that when peptone is introduced into the peritoneal cavity it has no effect on the coagulability of blood. Certain snake-poisons, thrombo-kinase, or nucleo-protein, and the artificially synthesised celloids of Grimaux, which give many of the colour reactions of protein bodies, will all in various doses induce intra-vascular clotting. Albino rabbits and the Norwegian hare in winter-time are generally regarded as immune to an injection of the last two bodies (Pickering), but, as E. H. Starling has pointed out, the statement is inaccurate for albino animals.

The injected peptone is a digestive product, obtained by the action of trypsin. It is a mixture of albumoses and probably other less-known substances. Pick and Spiro consider that a heat-resistant body, peptozym, which is without influence upon extra-vascular blood, is the essential agent which affects intravascular plasma. The behaviour of peptone-plasma is inconstant. It may clot after a time spontaneously, but may do so quickly or not at all. Witte's peptone, in doses below 2 centigrammes per kilo body-weight, hastens coagulation, but above this dose it exerts a retarding influence (W. M. Thompson[1]). Water, weak acetic acid, or a stream of carbon dioxide, induces coagulation in peptone-plasma, even when this is free from leucocytes (Wooldridge). From a mass of conflicting statements it would appear that peptone-plasma contains thrombogen, kinase, and calcium ions, but no thrombin. It is probable that, like normal plasma which contains some anti-thrombin, an excess of this substance is present, and its development is due to a reaction of the organism following the introduction of peptozym. That anti-kinase is also present is doubtful, since

[1] *Journal of Physiology*, vol. xx. 1896.

the plasma easily clots on the addition of tissue-extract. The development of anti-thrombin is apparently bound up with the function of the liver. If this is shunted out of the circulation, peptone, on injection, is without influence on the coagulability of the blood, though if only the lymphatics of the organ are ligatured, peptone, as Starling and Delezenne have shown, still produces its effect. The artificial perfusion of the liver, but of no other organ, with a fluid containing peptone, yields an anti-coagulant substance, not because this is formed directly from the peptone, but from the liver-cells as a specific product of reaction. A complete explanation of the effect of peptone is at present not possible. It resembles the plasma of birds, except that in these animals thrombo-kinase is absent. An injection of peptone into the goose yields a blood with a marked amount of anti-thrombin. Such blood clots easily with kinase, but with difficulty on the addition of thrombin or goose serum. In this respect the effects of peptone injection are less marked in birds than mammals (Fuld).

8. The Intravenous Injection of Thrombo-Kinase

An injection of kinase may, according to the animal and the dose, yield a blood from which a kinase-plasma may be obtained that clots slowly or not at all. The introduction of this substance, as already mentioned, may cause intra-vascular clotting, but the organism, as the observations of Wooldridge, Groth, and Wright have shown, undoubtedly can cope with and neutralise the effects that would occur if thrombin, as such, circulated in the blood. When clotting is induced, as Wright[1] first pointed out by experiments on animals rendered either apnœic or asphyxiated, the presence of carbon dioxide in the blood is one of the deciding factors. Essential differences have been pointed out by Boggs between peptone- and kinase-plasma. Dilution with water, addition of acid, or addition of calcium chloride does not induce the latter to coagulate. When the action of thrombin upon kinase-plasma is contrasted with its behaviour towards peptone-plasma, it can be seen that coagulation occurs readily in the former, but with difficulty or not at all in the latter, while other experiments have shown that

[1] *Journ. of Physiol.* xii. 1891.

kinase-plasma does not readily clot when treated with thrombokinase. Moreover, Wooldridge some years ago pointed out that kinase-plasma could be easily coagulated by the addition of peptone-plasma. The plasmata obtained by injection are therefore dissimilar in many respects; in peptone-plasma an anti-thrombin predominates, in kinase-plasma an anti-kinase.

9. Substances which directly Hinder Coagulation both inside and outside the Body

Substances such as hirudin, which is the active principle secreted by the salivary glands of the medicinal leech, a similar body obtained from the heads of other blood-sucking worms, such as ankylostoma caninum, as well as the virus of many thanatophidia, together with anti-bodies, such as those described by Pugliese[1] and extracted by him from the blood and almost every organ of the body except the brain, directly check the coagulation of blood both inside and outside the organism.

The anti-body or bodies are, according to Pugliese, chiefly obtained from the liver, kidneys, and muscles. They are not destroyed by heat, but are diffusible. His results may be easily seen in the following table:

						Clot.
Plasma	+	Anti-bodies	+	Ca.	=	o
„	+	„	+	H_2O	=	o
„	+	„	+	Serum	=	+
„	+	„	+	Kinase	=	+

It would seem therefore as if both anti-kinase and anti-thrombin were capable of being yielded by nearly all the tissues of the body. The inner coat of arteries, which might have been expected to form anti-bodies during life, have, however, been shown by Loeb[2] to yield no anti-bodies of any kind.

The term "hirudin" was introduced by Jakoby and Franz. This substance appears as yellowish scales soluble in water with a slight turbidity, and the activity of the solution is not destroyed by boiling. Its activity is such that a definite amount, 0·01 gr., will maintain 7·5 cc. of blood fluid outside the body. The researches of Fuld and Spiro show that hirudin can undoubtedly neutralise thrombin both within and outside the

[1] Quoted from *Centralbl. f. Physiologie*, 1906.

[2] *Virch. Archiv.* clxxvi. 1904, and *Hofmeister's Beiträge*, v. 1904.

body, but only in certain proportions. Pekelharing considers that its action depends upon hindering the formation of proferment, *i.e.* kinase, from the corpuscles of blood, but this is improbable, since in hirudin-blood all the corpuscles are particularly well preserved, and on cooling the plasma no separation of any granular precipitate can be noticed. The differences between hirudin-, peptone-, oxalate-, and fluoride-plasma can be seen in the following table, from which it may be concluded that in the case of hirudin this substance does not remove lime nor neutralise any kinase:

		Clot.
Peptone-plasma	+ Weak acetic	= +
„	+ Water	= +
Oxalate-plasma	+ Calcium	= +
Fluoride-plasma	+ Calcium	= o
„	+ H_2O	= +
Hirudin-plasma	+ H_2O	= o
„	+ Calcium	= o
„	+ Acetic acid	= o
„	+ Kinase[1]	= + or o

Hirudin, therefore, exerts its effects by neutralisation of any thrombin which may appear. Fuld and Spiro have also shown that no neutralisation-ratio exists between thrombo-kinase and hirudin. Schittenhelm and Bodong do not hold this view, since a solution of fibrinogen containing calcium salts is not prevented from clotting by hirudin, and in the case of hirudin-blood the action is set aside by a definite amount of thrombo-kinase. These authors also draw attention to the fact that a suspension of blood-platelets, which after a time spontaneously gelatinises, does not pass into this state when hirudin is present. Hirudin-blood has also been shown to be markedly resistant to putrefactive change, possibly owing to the liberation of alexines from the leucocytes.

Among snake-poisons, the anti-coagulant effect of cobra-virus is set aside by the anti-venom prepared by Calmette, and Morawitz has shown that the action of the venom is dependent on the existence of an anti-kinase.

[1] Depends on the amount of thrombin produced in relation to amount of hirudin present.

10. Morphology of Blood-coagulation

Recent papers of Loeb on the process of coagulation in vertebrate blood, those of Ducchesi, Bürker, and more recently Nolf, deal with this part of the subject. Loeb, whose view corresponds in some respects to that of Nolf, who worked with the blood of vertebrates, distinguishes two distinct phases in coagulation:

1. The stage of agglutination of leucocytes in arthropoda and crustacea, and of blood-platelets in mammals.

2. The formation of fibrin from this agglutinated stage.

Loeb finds that peptone does not hinder clotting in the lobster, neither does kinase from vertebrates induce coagulation in the blood of invertebrates. In the blood of *Limulus* he states that a fibrinogen coagulable at 56° does not exist, and that this temperature does not interfere in any way with the first stage of coagulation. On dilution with water the blood of this animal shows agglutination of leucocytes, and the remaining liquid clots easily on the addition of muscle-extract from the same animal.

The macroscopic appearances on glass in shed blood to which Ducchesi[1] has drawn attention as the first alteration which blood undergoes outside the body, is due to an accumulation of platelets, and is a phenomenon entirely absent in peptone or hirudin-blood. This is also a definite agglutination process. Every observer, however, has seen that the bodies termed "platelets" are preserved in both these fluids. But agglutination rarely occurs. Regarded purely from the morphological point of view, it is possible that both inside and outside the body any damage to the blood-plasma is followed firstly by production and secondly by agglutination of previously non-existent platelets,[2] and then this stage is succeeded by the subsequent appearance of fibrin. As far as the relation of these phases to the coagulation process is concerned, this view is similar to that recently proposed by Bürker.

[1] *Hofmeister's Beiträge*, iii. p. 378.

[2] I am able to confirm a recent observation of Marino (*Comptes rend.* No. 4, 1905), who observed that when rabbits' blood is received into so much absolute alcohol that this is only slightly diluted, no platelets can be demonstrated to exist. It is inconceivable that they are destroyed, since the same blood mixed with 95 per cent. alcohol yields an abundant supply. This experiment, therefore, lends no support to the view that platelets exist in undamaged circulating blood.

Nolf's[1] recent contributions can scarcely be said to simplify the coagulation question. Besides the salts of calcium, he recognises three protein bodies which are concerned in the formation of a clot:

1. A protein derived from the leucocytes, termed leucothrombin.

2. One found in the liver—hepatothrombin.

3. Fibrinogen, which is formed by the activity of the cells of the same organ.

The interaction of the first two with calcium yields fibrinferment. Thrombin arises by the formation of an envelope of hepatothrombin around fine particles of leucothrombin, which appear early in a clear, spontaneously coagulable liquid. This process is followed by gelatinisation of the plasma, owing to the further aggregation of another layer of fibrinogen upon the thrombin. Fibrin, therefore, originates from an agglutination process which becomes established in a liquid plasma which at first shows no morphological constituents, and the whole phenomenon of coagulation is to be regarded as one of agglutination which takes place in a perfectly clear plasma which is originally devoid of any morphological constituents.

[1] *Archiv Internat. de Phys.* iv. 1906.

PROTEIN METABOLISM

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In an earlier number of this journal Dr. F. Gowland Hopkins, of Cambridge, in an interesting paper, drew attention to the important and interesting subject of the utilisation of the protein moiety of the food. As he fully discussed the subject in its general bearings, I do not wish to do more than draw attention to the advances which the more recent work has made in our knowledge of the various changes which proteid undergoes before absorption, and, in a brief fashion, to refer to the probable fate of the various fractions after such absorption has taken place.

Before, however, we can gain any insight into this profound problem, the question of how, and in what form, the protein is absorbed must be definitely determined.

Formerly it was universally held that protein was absorbed after digestion in the form of albumoses and peptones, which were immediately converted into albumen, and the whole subject was then dismissed. The work of the past few years has shown that this cut-and-dry statement is by no means justified, and that the problem is of a much more complicated nature.

Before dealing with the absorption of the hydrolysed, *i.e.* the digesten proteid, it would be well to consider the absorption of unaltered, undigested, or native proteins, as they are called.

The work of many investigators, both in Germany and elsewhere, has demonstrated beyond cavil that native protein injected into the blood stream can be utilised to a certain extent—indeed, the recent work of Sollmann and Brown[1] has shown that under favourable conditions egg albumen injected intravenously can be well utilised; in many instances only a

[1] Sollmann and Brown, *Journ. of Exper. Med.* 6, 407.

mere trace is excreted through the kidney. How and where this utilisation takes place is as yet unknown.

The classical work of Miescher on the Rhine salmon demonstrated the fact that the body can change one protein substance into another without the intervention of the intestinal wall. This observer stated that after the fish entered the fresh water they ceased to take food, and yet in spite of this, great anabolic changes took place in the salmon body. These changes consisted in the marked growth of the generative organs, which was shown to take place at the expense of the muscular system.

As regards the absorption of native proteins from the intestine, the old work of Voit and Bauer,[1] which showed that absorption of undigested proteins such as serum and egg albumen could take place, has been extended and confirmed by Heidenhain,[2] Friedländer,[3] Waymouth Reid,[4] and others. Ascoli,[5] with the newly introduced biological methods of testing for the presence of proteins, has been able to prove that the protein taken up is unchanged, and can give the precipitin reactions significant of the protein introduced. The absorption of unchanged protein can hardly, however, be said to occur under normal conditions. In the experiments referred to the protein was introduced in excess into the intestine. This absorption would seem also to be dependent to some extent on an increased permeability of the intestinal wall, such as is found in the very young. Another factor which plays an important part in this form of absorption is the presence of water, or salt solution. Friedländer (*l.c.*) has shown that after all the water or salt solution has been taken up, absorption of the protein, to all intents and purposes, comes to a standstill.

The objection which has naturally been raised to these various experiments is that, although the observers say that the intestine used in the experiment was thoroughly washed out previous to the introduction of the protein, yet there may have been sufficient trypsin left to act on the protein, and

[1] Voit and Bauer, *Zeit. f. Biol.* v. 536, 1869.
[2] Heidenhain, *Pflüger's Archiv*, 56, 1894, 579.
[3] Friedländer, *Zeit. f. Biol.* 33, 1896, 264.
[4] Waymouth Reid, *Phil. Trans.* Ser. B. 192, 1900, 21.
[5] Ascoli and Vigan, *Zeit. f. physiol. Chem.* 39, 1903, 283.

thus bring about its absorption in what might might be termed a natural fashion. This objection can, however, be dismissed (1) owing to the rapidity of the absorption which has been observed, and (2) because the amount of enzyme left after the cleansing of the intestine must be very small indeed. The figures obtained by Heidenhain (*l.c.*) and Waymouth Reid (*l.c.*) showed that the intestine could deal with quite large amounts of serum in a comparatively short time. It is impossible to understand how the trace of trypsin, supposed to be present, could bring this about, more especially as trypsin does not act by any means rapidly on this form of protein in its native state.

How then is the protein normally absorbed? Protein foodstuffs after ingestion are first of all acted on in the stomach by the pepsin present; here, however, under normal conditions decomposition is not fully carried out. This gastric digestion seems to aid the final action of the trypsin in some way other than the mere mechanical aid given by rendering the more or less solid masses of foodstuff suitable for the rapid attack of the trypsin and other intestinal enzymes. Abderhalden and Fischer[1] have shown that protein stuffs which have been digested first by pepsin and then by trypsin, yield, *in vitro* at least, a much smaller amount of polypeptide substance than do the same proteins when they have been subjected to the action of trypsin alone. Further, Abderhalden and Rona[2] have demonstrated, by feeding experiments on mice, that the digest which arises from the combined action of pepsin and trypsin has not the same power of preventing loss of nitrogen—in other words, has not the same food value as the products yielded by trypsin alone. On the other hand, from the experiments of Czerny and others one might conclude that the stomach is a quite unnecessary organ. They have shown that animals from whom the stomach has been practically completely removed can not only exist, but after they have accustomed themselves to the new conditions can actually thrive. The food from the stomach is passed on into the small intestine, where it is more or less completely broken down by the action of the trypsin into simpler bodies—into albumoses, peptones, and bodies which no longer give the biuret reaction. The

[1] Abderhalden and Fischer, *Zeit. f. physiol. Chem.* 40, 1904, 215.
[2] Abderhalden and Rona, *Zeit. f. physiol. Chem.* 42, 1904, 528.

albumoses and peptones, as Cohnheim[1] has shown, can be resolved into simpler bodies—the amino acids, by the action of a ferment (erepsin) discovered by him in the intestinal mucous membrane. This ferment, it may be stated, does not attack native proteins with the exception of casein.

The important question which is now awaiting solution is whether it is necessary that the protein be so far decomposed before it can be utilised by the body tissues for transformation or resynthesis into the complex body proteins. Many observations on this point have been carried out by investigating the contents of the intestinal canal of animals killed a few hours after a full meat meal. This method, however, has the serious drawback that both the decomposition of the protein and the absorption of the products go constantly on together, thus no time is allowed for any accumulation of the products in the gut. Further, it is quite possible that some of the products formed may be more readily absorbed than others, and in this way the material which is eventually obtained from the intestine may not give a true indication of the real nature of the decomposition. Kutcher and Seemann[2] have carried out such experiments, and have demonstrated in the intestinal contents the presence of quite a number of the well-known decomposition products. They were able to isolate leucin, tyrosin, lysin, and arginin, thus both mono- and di-amino acids. Abderhalden[3] has also investigated this question along the same lines. He was able to isolate from the intestinal contents by Fischer's ester method alanin, leucin, glutamic and aspartic acids, and perhaps traces of *a*-proline and phenyl-alanin. Tyrosin was also found. Some polypeptide was also present, and yielded on hydrolysis with acid glycocoll, *a*-proline, and phenylalanin.

A very important point was made a few years ago when O. Loewi[4] proved that animals which were fed on the decomposition products of proteins, obtained by prolonged digestion with trypsin until complete disappearance of the biuret reaction, could be kept alive. Not only did he keep the animals alive with these products as the sole source of their supply of

[1] Cohnheim, *Zeit. f. physiol. Chem.* 33, 1901, 451.
[2] Kutscher and Seemann, *Zeit. f. physiol. Chem.* 34, 1902, 528.
[3] Abderhalden, *Zeit. f. physiol. Chem.* 44, 1905, 617.
[4] Loewi, *Schmiedeberg's Archiv*, 48, 1902, 303.

nitrogen, but they actually retained a percentage of the nitrogen given. An interesting fact was brought out in the course of these observations as regards the calorific value of the decomposition products. A calorimetric estimation of one gramme of products was carried out by Rubner, with the result that this amount was found to equal 4·599 cal., thus very similar to the figure for albumen. There must be given, along with these decomposition products, an abundant supply of carbohydrate food in the form of sugar and starch. Recently Lüthje[1] has proved that it is absolutely essential that the animal get carbohydrates, and further, that these carbohydrates cannot be replaced by fat in the diet. The fact that Lesser,[2] who denied the correctness of Loewi's work, only used fat and no carbohydrates, probably fully explains his negative results. Loewi's results have been fully confirmed by other workers, such as Henriques and Hansen, Abderhalden, and others. Henriques and Hansen[3] not only were able to confirm Loewi's results, but showed further that only a fraction of the products produced by pancreatic digestion could keep the animal alive. They found that those products which were soluble in alcohol sufficed, whereas the insoluble fraction was quite inert. Again, they showed that the part of the digest not precipitated by phosphotungstic acid, that is the so-called monamino acid fraction, had the nutritive value; here, again, the part precipitated was of no use as a food. This statement, that a part merely of the products suffices as a food, has been fully confirmed by Lüthje (*l.c.*), always supposing, however, that there be a plentiful supply of carbohydrate food in addition. In this respect the animal body closely approximates the vegetable kingdom, where it has been shown that carbohydrates play a very important part in the protein synthesis. Abderhalden[4] and his co-workers have also confirmed and extended Loewi's results. As I have already mentioned, differences were found between the nutritive values of protein digested by trypsin alone and by pepsin followed by trypsin. They, like Henriques and Hansen, found that although the products arising from enzyme action were effective, those which were

[1] Lüthje, *Pflüger's Archiv*, 113, 1906, 547.
[2] Lesser, *Zeit. f. Biol.* 45, 1904, 497.
[3] Henriques and Hansen, *Zeit. f. physiol. Chem.* 43, 1904, 417.
[4] Abderhalden and Rona, *Zeit. f. physiol. Chem.* 44, 1905, 198.

obtained by hydrolysis with acid were of no use. In a recent paper, it is true, Henriques and Hansen[1] have shown that the acid products can act to some extent as sparers of protein. How, then, do the acid hydrolysis products differ so much in this vital action from the products obtained by digestion with ferments? Is it that by the more active boiling acid products which are of absolute necessity for the maintenance of life are too far broken down, or is it perhaps due, in part at least, to the racemisation which takes place? One series of bodies which are known to be formed in tryptic digestion, and not during acid hydrolysis, the polypeptides—bodies formed by the linking together of two or more amino acids—cannot play any part, as it has been shown (Henriques and Hansen) that when they were removed by precipitation the monamino acids which were left sufficed. Whatever the cause, the main fact still stands that animals fed with acid hydrolysis products perish, whereas animals fed with ferment digest products not only live, but may even thrive on them.

As regards the statement that the products of protein digestion were absorbed in the form of albumoses and peptones, it rested mainly on the work of Salvioli,[2] carried out many years ago. This worker stated that if he isolated a loop of intestine, and into it put the products in question (albumoses and peptones), on perfusion with blood he found that they disappeared. Further, Salvioli was unable to detect them in the blood used for perfusion, therefore he concluded that the absorbed products were regenerated to more complex bodies before they reached the blood. Recently the writer, working in conjunction with Dr. Leathes,[3] repeated the work of Salvioli, and found that albumoses and peptones introduced into the loop of intestine did indeed disappear, but the interpretation, supported by analytical data, was quite other. We found that the peptone, etc., introduced into the loop was merely split up into simpler bodies which do not give the biuret reaction, in all probability due to the action of the ferment erepsin. If it be due to the erepsin, then this ferment could not have acted intracellularly as Cohnheim holds, as so far as we could

[1] Henriques and Hansen, *Zeit. f. physiol. Chem.* 49, 1906, 113.
[2] Salvioli, *Du Bois Reymond's Archiv*, 1880, Suppl. p. 95.
[3] Cathcart and Leathes, *Journ. of Physiology*, 33, 1906, 462.

estimate no absorption took place. Of course, as Salaskin[1] and Cohnheim himself have shown, there is a small quantity always to be found free in the lumen of the gut.

Very contradictory statements exist as to whether albumoses and peptones are ever normally present in the blood. One had come to believe that there was no evidence of their presence in this fluid, but a year or two ago definite statements that albumoses had been detected were published by well-known workers. The results were not always positive, however, even with blood examined during the absorption of proteins. Embden and Knoop,[2] and later Langstein,[3] stated definitely that they had managed to prove that albumoses were among the normal constituents of normal blood. This statement has been denied by Abderhalden and Oppenheimer,[4] these workers maintaining that it is not a normal constituent even under the most favourable conditions. For instance, three dogs which had been starved for several days were given a full meat meal, and then, six to eight hours later, were killed. On examination no trace of a biuret-giving substance was found in the blood thoroughly freed from its protein. They suggest that the positive results have been probably due to traces of protein left owing to imperfect coagulation. Howell,[5] in a recent paper, came to the same conclusion after having carried out many experiments with a fairly large series of animals at different periods of digestion. The method he employed was one of dialysis through membranes permeable to albumoses and peptones, but not to the serum proteins.

If the absorption takes place in the form of the amino acids, which are soluble bodies, one would expect on examination of the blood to find, after a full protein meal, a very definite increase in the amount of non-precipitable or soluble nitrogen. This, however, does not turn out to be the case, as Dr. Leathes and the writer (*l.c.*) have shown that there is an increase, but it is not very great. Of course, when one considers the rapidity of the blood flow through the intestinal vessels, it is perhaps rather to be wondered at that any evidence

[1] Salaskin, *Zeit. f. physiol. Chem.* 35, 1902, 419.
[2] Embden and Knoop, *Hofmeister's Beiträge*, 3, 1902, 120.
[3] Langstein, *Hofmeister's Beiträge*, 3, 1902, 373.
[4] Abderhalden and Oppenheimer, *Zeit. f. physiol. Chem.* 42, 1904, 153.
[5] Howell, *Amer. Jour. of Physiol.* 17, 1906, 273.

of increase at all was obtained in the comparatively small amount of blood which could be examined. Abderhalden (*l.c.*) attempted to prove the presence of amino acids in the blood after a full proteid meal, but without success. The method which he employed was the very excellent one devised by Fischer, in which the amino acids, even when present in small amount, form crystalline compounds with β-naphthalinsulphochloride. Howell (*l.c.*), by using this same method in conjunction with a process of dialysis, has reported that he has been able to detect small amounts of amino acids in the blood taken from dogs at the height of digestion; more, further, in the portal blood than in blood taken from the general systemic circulation. Even in the blood of dogs which had fasted for a considerable number of hours, a positive reaction could still be obtained.

A point in favour of the full breakdown of the protein molecule was given in a piece of work by Abderhalden and Samuely,[1] in which an attempt was made to affect the constitution of serum protein. A horse was bled to an extreme degree, and then was fed with a protein obtained from wheat—gliadin. This protein differed very markedly from the constitution of the serum protein, especially in its content of glutaminic acid (gliadin has 36·5 per cent. glutaminic acid, whereas serum albumen has only 7·7, and serum globulin 8·5). When the horse on the gliadin diet had regenerated its blood to a large extent, it was again bled, and the constitution of the newly formed serum proteid investigated. Results, as regards the alteration of the internal constitution of the body protein by the nature of the food protein, were quite negative. The serum protein obtained resembled that formerly present in every respect. The fact, too, that Howell (*l.c.*) was able to detect amino acids, but no trace of albumoses or peptones in the blood, seems to lend support to the view that the hydrolytic changes in the intestine are pretty thorough.

In what form, then, does the absorbed protein reach the tissues proper? Is it absorbed as simple amino acids in solution absolutely unchanged? In all probability not to any great extent, as is shown by the slight increase of the nitrogen in the blood. Of course, it might be absorbed by means of the leucocytes, as suggested by Hofmeister, and that owing to

[1] Abderhalden and Samuely, *Zeit. f. physiol. Chem.* 46, 1905, 193.

the methods of analysis employed it was not detected. On the other hand, these amino acids can lose their nitrogen fairly readily through the action of the body tissues, as has been demonstrated by the work of Jacoby[1] and of Lang.[2] Lang showed that if one mix various amino acids with chopped-up animal tissue, such as liver, spleen, intestine, etc., the amino groups are split off. For instance, glycocoll was found to give up its nitrogen freely when mixed with liver, but even more freely when in contact with intestinal tissue. Tyrosin could be attacked by the liver, but only with difficulty. Leucin, on the other hand, was fairly readily decomposed by that organ, and so on with other amino acids. Thus it may be that the absorption of the decomposition products is in the form of bodies nitrogen free, as acids of the fatty acid series such as lactic acid. In favour of this view, perhaps, the work of Nencki and his co-workers may be cited. Nencki, Pawlow, and Zaleski[3] showed that the blood taken from the portal system contains three to four times more ammonia than the systemic arterial blood. This is extremely well marked where the animal has previously been fed on a meat diet. This ammonia might be regarded as that split off from the amino acids during or after their course through the intestinal wall, and which, for the most part, is being hurried to the liver, there to be converted into urea for excretion. It must be remembered, however, that according to Horodynski, Salaskin, and Zaleski[4] starvation has practically no effect on the amount of ammonia in the arterial blood, and that there is only a very slight reduction in the amount present in the portal blood.

Others, again, hold that there is no such simple absorption, but that as soon as they are absorbed the products of digestion undergo synthesis, and in this reperfected form reach the body circulation. As regards this question of regeneration of a coagulable protein, Dr. Leathes and the writer (*l.c.*) were quite unable to detect any such increase, although this question was carefully gone into. Neither by an estimation of the total nitrogen before and after absorption nor by controls carried out by observations on the amount of hæmoglobin, were we

[1] Jacoby, *Zeit. f. physiol. Chem.* 30, 1900, 149.
[2] Lang, *Hofmeister's Beiträge*, 5, 1904, 321.
[3] Nencki, Pawlow, and Zaleski, *Schmiedeberg's Archiv*, 37, 1896, 26.
[4] Horodynski, Salaskin, and Zaleski, *Zeit. f. physiol. Chem.* 35, 1902, 246.

able to prove an increase. Kutscher and Seemann (*l.c.*) were unable, in their experiments, to find the crystalline products which they isolated from the contents of the intestine during digestion, either in the intestinal wall or in the blood. They discovered, however, in the wall of the intestine biuret-free extractive bodies which, on treatment with boiling acids, yielded leucin. They drew the conclusion from this observation that the leucin (and probably other crystalline products) absorbed from the canal is linked up with some other substance or substances into bodies of a more complex nature in the intestinal wall. Embden and Knoop (*l.c.*) were quite unable to prove that any synthetic action ever took place in the walls of the small intestine, when working, at any rate, with surviving gut outside the body. This is quite the reverse of what Glaessner[1] claimed to have found in the case of the gastric mucous membrane. This worker stated that, as Hofmeister[2] had previously found, if the albumoses present at the time of digestion be allowed to remain in contact with the isolated mucous membrane of the stomach, they for the most part disappear as such, and that in their place appears a coagulable protein body. Concerning the nature of this protein Glaessner says nothing, but holds its formation to prove that by the alteration of the albumose a synthesis has taken place. Objections have been raised to this work, and Cohnheim has held that the results noted by Glaessner may be due to differences in the case of coagulability of absolutely fresh protein of the mucous membrane, and of that which has been out of the body for some little time. Salaskin[3] offered as an explanation that the increase of protein may simply be due to a normal restitution of the cell protoplasm after its activity in ferment production.

Reference may be here made to a change which has been declared by some to be a true resynthesis—namely, to the formation of anhydride albumen, or plasteïn as it has been called. The curious property possessed by rennin of producing a precipitate—the plasteïn—in solutions of albumoses or peptones was first brought to notice by Okunew[4] in a Russian

[1] Glaessner, *Hofmeister's Beiträge*, 1, 1901, 320.
[2] Hofmeister, *Schmiedeberg's Archiv*, 19, 1885, 1.
[3] Salaskin, *Zeit. f. physiol. Chem.* 35, 1902, 419.
[4] Okunew (quoted by Sawjalow, *Pflüger's Archiv*, 85, 1901, 171).

publication. Kurajew[1] showed that the vegetable ferment papayotin possessed the same power of producing precipitates in albumose solutions. Later, another Russian observer, Sawjalow,[2] gave a fairly complete account of the various chemical properties of this body. Lawrow and Salaskin,[3] however, conceive this formation not to be a true regenerative process, nor a real example of synthetic action, and, further, hold that it is the result of digestion under what might be termed unfavourable conditions. Again, Herzog[4] and Volhard[5] believe that this so-called plasteïn formation is not the result of the action of rennin at all, but may be regarded as another example of the reversibility of reaction of proteolytic ferments (Herzog), or of pepsin (Volhard). As to whether it is due to pepsin or rennin does not seem to be of very great importance, especially as some of the more modern workers like Pawlow and Parastschuk[6] hold that the so-called peptic action and the so-called rennet action are merely two phases of action of one and the same ferment.

Another theory of resynthesis was brought forward many years ago by Ott,[7] Popoff,[8] and Brinck,[9] who held that albumoses and peptones injected into the stomach of a living animal, or of one just dead, are converted into protein bodies in the stomach wall. It was further asserted that the protein which was formed was serum albumen. Brinck put this action down as being brought about by a micro-organism, to which she gave the name of *Micrococcus restituens.*

Hofmeister,[10] as I have already mentioned, held that on absorption the peptone was taken up by the leucocytes, and then, either through their agency or through that of the adenoid tissue, it is converted into cell protoplasm. Heidenhain denied this hypothesis, but both he and Shore[11] held to

[1] Kurajew, *Hofmeister's Archiv*, 1, 1901, 121.
[2] Sawjalow, *Pflüger's Archiv*, 85, 1901, 171.
[3] Lawrow and Salaskin, *Zeit. f. physiol. Chem.* 36, 1902, 277.
[4] Herzog, *Zeit. f. physiol. Chem*, 39, 1903, 305.
[5] Volhard, *Munch. med. Wochsch.* 50, 1903, 2129.
[6] Pawlow and Parastschuk, *Zeit. f. physiol. Chem.* 42, 1904, 415.
[7] Ott, *Archiv f. Physiolog.* 1, 1883.
[8] Popoff, *Zeit. f. Biol.* 25, 1889, 427.
[9] Brinck, *Zeit. f. Biol.* 25, 1889, 453.
[10] Hofmeister, *Schmiedeberg's Archiv*, 22, 1887, 306.
[11] Shore *Journ. of Physiology*, 11, 1890, 528.

the opinion that there was a change from peptone into albumen, but instead of the adenoid tissue they accredited the reaction to the epithelial cells of the small intestine. On the other hand, as regards Hofmeister's statements as to the part the leucocytes played in the various assimilative processes, a good deal of work has been done. Pohl[1] showed that during digestion there was a very marked leucocytosis, and, further, he stated that there was an excess of leucocytes in the mesenteric veins over the corresponding mesenteric arteries during digestion of proteids. This latter statement was controverted by Paton, Goodall, and Gulland,[2] who stated that no difference could be detected between the two. Erdély[3] recently confirmed Hofmeister's statement that the intestinal wall is richer in leucocytes when the animal has been well fed than when a fasting animal is examined. Erdély even goes so far as to suggest that the nature of the leucocytosis varies with the changes in diet. Paton and his co-workers have also demonstrated that there is a true post-prandial leucocytosis in which the lymphocytes showed a marked percentage increase. There is also some increase in the polymorphs, but there is practically no change in the number of the eosinophiles. They differ, however, from Hofmeister as regards the site of origin of the leucocytes: instead of arising, as Hofmeister said, from the intestinal lymphatic tissue, Paton and Goodall[4] proved that the white cells came from the bone marrow.

[1] Pohl, *Schmiedeberg's Archiv*, 25, 1889, 31.
[2] Goodall, Gulland, and Paton, *Journ. of Physiology*, 30, 1903, 1.
[3] Erdély, *Zeit. f. Biol.* 46, 1905, 119.
[4] Goodall and Paton, *Journ. of Physiology*, 33, 1905, 20.

THE WORK OF EMIL FISCHER AND HIS SCHOOL ON THE CHEMISTRY OF THE PROTEINS

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The Proximate Constituents

The remarkable researches of Emil Fischer upon the chemistry of the proteins during the last few years, which are of no less magnitude than his classical work upon the Carbohydrates and the Purine Compounds, are of such great importance that it seems desirable to give a somewhat detailed account of these investigations and to indicate the methods by which Fischer has arrived at his results.

Commencing with a minute study of the amino acids, which result in such variety as the products of hydrolysis of the proteins, Fischer next turned his attention to their separation as they result by hydrolysis, whereby a new method was perfected, which is now known as the ester method; and finally he has made extraordinary progress in the most important stage of synthesis.

Fischer has lately published the results of his work from 1899 to 1906 in book form, the opening pages of which consist of a lecture delivered to the Deutsche Chemische Gesellschaft in Berlin in January 1906. His researches are divided into three parts:

I. The Amino Acids.
II. The Hydrolysis of the Proteins.
III. The Polypeptides.

It has been known for many years from the work of Kühne, Neumeister, Chittenden, Schulze, Hlasiwetz, Habermann and others that the amino acids are the keystones of the protein molecule. It will make it easier to follow Fischer's subsequent work if we here give a list of the amino acids which have been

obtained up to the present time, as also their constitution in so far as it is known.

(a) *Monoaminomonocarboxylic acids:*

Glycine or amino-acetic acid.
Alanine or *a*-aminopropionic acid.
Valine or *a*-aminoisovalerianic acid.
Leucine or *a*-aminoisocaproic acid.
Isoleucine or *a*-aminomethylethylpropionic acid.
Phenylalanine or phenyl-*a*-aminopropionic acid.
Tyrosine or *p*-oxy-phenyl-*a*-aminopropionic acid } oxyamino acids.
Serine or *β*-oxy-*a*-aminopropionic acid
Cysteine or *β*-thio-*a*-aminopropionic acid } thioamino acids.
Cystine or dicysteine, *a*-diamino-*β*-dithio-propionic acid.

(b) *Monoaminodicarboxylic acids:*

Aspartic acid or aminosuccinic acid.
Glutamic acid or *a*-aminoglutaric acid.

(c) *Diaminomonocarboxylic acids (hexone bases):*

Ornithine or *a*-δ-diaminovalerianic acid.
Lysine or *a*-ε-diaminocaproic acid.
Arginine or *a*-amino-δ-guanidine valerianic acid.
Histidine or *β*-imidazoleaminopropionic acid.

(d) *Diaminooxymonocarboxylic acids:*

Diaminotrioxydodecanic acid.

(e) *Heterocyclic compounds:*

Proline or *a*-pyrrolidine carboxylic acid.
Oxyproline or oxy-*a*-pyrrolidine carboxylic acid.
Tryptophane or indoleaminopropionic acid.

This list, appalling as it looks, is in reality comparatively simple, and is evidence also as to the great complexity of the proteins, which consist of a combination of these amino acids in various proportions.

I. The Amino Acids

The amino acids as they are obtained from the proteins are, with the exception of glycine, in the optically active form. The synthetical products, on the other hand, are inactive or racemic,

i.e. consist of a mixture of equal parts of the dextro- and lævo-rotatory varieties. The real synthesis of the natural compounds is, therefore, only attained when the synthetical substances have been separated into their two constituents. Two methods may be used for this purpose: the biological method—destroying the one isomer by means of micro-organisms, such as *Penicillium glaucum* and *Aspergillus niger*—had been used by Schulze and Bosshard to obtain leucine and glutamic acid, and by Engel to obtain aspartic acid; but the chemical method of combining with optically active compounds to form salts and fractionally crystallising these salts had not been employed with any success. This was probably due to the small affinity which the simple monoamino acids have for acids and bases. The aminodicarboxylic acids, on the other hand, are moderately strong acids, which combine with bases to form salts of this kind, but the desired results were not achieved in the attempts thus made to separate the optically active forms.

Fischer found that by preparing the benzoyl derivatives of the amino acids, their acidic character was greatly increased and that they then formed with the optically active bases—strychnine, brucine, and morphine—stable salts which were soluble with greater difficulty than the amino acids and more easily isolated. Hippuric acid, or benzoylglycine, has been known for a long time; the derivatives of the other amino acids are similar in constitution. The ordinary process of benzoylating by the Schotten-Baumann method in the presence of excess of caustic soda gave poor yields of the benzoyl derivatives of the amino acids, but by substituting sodium bicarbonate for the caustic soda and using a large excess of benzoylchloride Fischer obtained excellent results, and succeeded in preparing the optical isomers of alanine, leucine, tyrosine, phenylalanine, aspartic and glutamic acids, as also of *α*-aminobutyric acid and *α*-amino-*n*-caproic acid.

For the preparation of large quantities of optically active amino acids, such as is required in the synthesis of the proteins, the benzoyl method for the separation of the isomers was not found to be convenient on account of the fact that the reconversion into the amino acid was often carried out with difficulty, since it required a long time and large quantities of acid (100 times the quantity of 10 per cent. hydrochloric acid) to completely hydrolyse the compound. Fischer had therefore to

discover another method. This consisted in the preparation of the formyl derivative by heating the amino acid with anhydrous formic acid at 100° C.; the separation of the inactive compound into its optically active isomers was again effected by means of the brucine salts; and finally the hydrolysis of the formyl compound was performed by heating for one and a half hours with ten times its quantity of 10 per cent. hydrochloric acid. Large amounts of active leucine and valine have thus been obtained. The optically active components of the latter compound, *a*-aminoisovalerianic acid, were first prepared by this method.

Quite lately Fischer and Jacobs have separated serine into its two optical isomers; neither the benzoyl derivative nor the formyl derivative gave the desired result, but they were successful when they used the *p*-nitrobenzoyl compound. Still more recently, the optically active forms of isoserine and diaminopropionic acid have been prepared.

It might be here mentioned that the biological method of separating the optically active compounds of the amino acids has recently been carried out by F. Ehrlich, who employed yeast in his experiments instead of the usual moulds.

In order to obtain the optically active amino acids, the racemic compound must first be synthesised. Two methods are generally employed for this purpose:

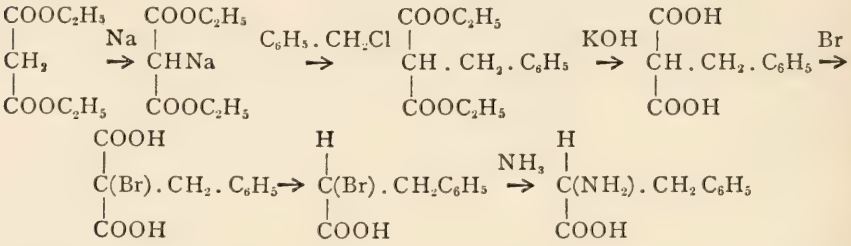
(1) The action of ammonia on the halogen fatty acid.

(2) The combination of aldehydes with hydrogen cyanide and ammonia and the subsequent hydrolysis of the amino-cyanohydrin.

Fischer has made use of both these methods: by the first method he prepared *a*-aminobutyric acid, *a*-amino-*n*-caproic acid, valine, and *a*-amino-*n*-valerianic acid. The latter two amino acids were also synthesised by the second or Strecker's method, by which isobutyl-*a*-aminoacetic acid or leucine was prepared from isovaleraldehyde. The identity of the benzoyl compound with that from natural leucine, as obtained from proteins and for a long time erroneously supposed to be *a*-amino-*n*-caproic acid, definitely proved the constitution of this amino acid, which had already been pointed out by E. Schulze and Likiernik in 1891, but had not been generally recognised.

Fischer has extended the first method by introducing a new mode of preparing the *a*-halogen fatty acid. This consists in

brominating the monoalkylmalonic acid, which, on heating, loses carbonic acid and is converted into the bromo fatty acid. Leucine can be readily prepared by this method from isobutylbromide and malonic ester; this method is especially useful for the synthesis of phenylalanine which is carried out by the following stages:



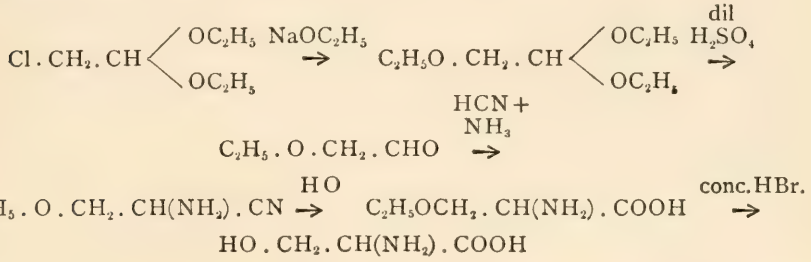
Isoleucine, which was discovered by F. Ehrlich in 1904 in beetroot residues, and later as a product of hydrolysis of proteins, is isomeric with leucine, but is not identical with the *a*-amino-*n*-caproic acid. Ehrlich considers it has the constitution of *a*-aminomethylethylpropionic acid $\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>\!CH.CH.NH_2.COOH$ on account of its synthesis from *d*-amylalcohol, which was oxidised to *d*-valeraldehyde and then combined with hydrogen cyanide and ammonia, according to the second method of preparation; further, it gives *d*-amylalcohol on fermentation, whereas leucine gives isoamylalcohol. Bouveault and Locquin have also synthesised an *a*-aminomethylethylpropionic acid which appears to be identical with Ehrlich's isoleucine.

Tyrosine was not prepared by either of the above methods; benzoyltyrosine, as first synthesised by Erlenmeyer and Halsey by the reduction of *p*-oxy-*a*-benzoylaminocinnamic acid obtained from hippuric acid and *p*-oxybenzaldehyde, was employed by Fischer for the separation of the optically active isomers.

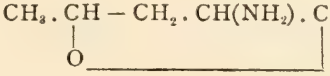
The second method was employed for the synthesis of the oxyamino acids. Serine, discovered by Cramer in 1864, is the simplest representative of this series, and was obtained by Fischer and Leuchs from glycollic aldehyde, hydrogen cyanide, and ammonia. Not only did this synthesis serve to definitely establish the constitution of serine, but it was the first instance of the employment of Strecker's method to build up oxyamino acids from oxyaldehydes. The constitution of serine was determined a little later by Erlenmeyer by a different method. It

was thus proved to be *a*-amino-*β*-oxypropionic acid, the isomeric compound, isoserine, being *β*-amino-*a*-oxypropionic acid.

Leuchs and Geiger have since found a better method for the synthesis of serine, from chloracetal, which is best described by the following formulæ:


Cl . CH₂ . CH(OC₂H₅)(OC₂H₅)
NaOC₂H₅
C₂H₅O . CH₂ . CH(OC₂H₅)(OC₂H₅)
dil H₂SO₄
HCN + NH₃
C₂H₅ . O . CH₂ . CHO
HO
C₂H₅ . O . CH₂ . CH(NH₂) . CN
C₂H₅OCH₂ . CH(NH₂) . COOH
conc. HBr.
HO . CH₂ . CH(NH₂) . COOH

By the same method Fischer and Leuchs have prepared *a*-amino-*γ*-oxyvalerianic acid, a compound which behaves like the other *γ*-oxy acids in easily forming an anhydride or *γ*-lactone giving the base



This substance readily polymerises to a diketopiperazine, a condensation made much use of in the synthesis of proteins.

Like the oxyaldehydes, the carbohydrates combine with hydrogen cyanide and ammonia; thus, *d*-arabinose gives *d*-glucosaminic acid, which is identical with the product obtained by the oxidation of glucosamine. Fischer and Leuchs were by this means able to determine the constitution of this important compound.

The oxyamino acids, according to Fischer, are of extreme importance on account of their relationship on the one hand to the carbohydrates and on the other hand to the proteins, in which they probably occur to a much larger extent than is at present known.

Another oxyamino acid, δ-oxy-*a*-aminovalerianic acid, has been synthesised by Sörensen, by a method similar to that employed by Fischer in the synthesis of the diamino acids. It is isomeric with Fischer's *a*-amino-*γ*-oxyvalerianic acid, and constitutes another member of the series of the oxyamino acids.

Compared with the monoamino acids the diamino acids are much more difficult to obtain synthetically. The only diamino

acid prepared by synthesis before Fischer commenced his researches was diaminopropionic acid, which was obtained by Klebs in 1894 by the action of ammonia on dibrompropionic acid. The similar reaction with *a*-δ-dibromvalerianic acid did not lead to the synthesis of the expected diamino acid, but to the formation of *a*-pyrrolidine carboxylic acid (Willstätter, 1900).

By making use of Gabriel's phthalimide method for synthesis with a slight modification Fischer prepared *a*-δ-diaminovalerianic acid. The series of reactions occurring in the process are as follows:

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle NK + Br.CH_2.CH_2.CH_2Br + Na.CH\langle\begin{matrix}COOC_2H_5\\COOC_2H_5\end{matrix}$$

$$= NaBr + KBr + C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle N.CH_2.CH_2.CH_2.CH\langle\begin{matrix}COOC_2H_5\\COOC_2H_5\end{matrix}$$

Bromination then gives

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle N.CH_2.CH_2.CH_2.C\begin{matrix}\diagup COOC_2H_5\\ -Br\\ \diagdown COOC_2H_5\end{matrix}$$

which, on hydrolysis and loss of carbon dioxide on heating, passes into phthalimidobromvalerianic acid:

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle N.CH_2.CH_2.CH_2.C\begin{matrix}\diagup H\\ -Br\\ \diagdown COOH\end{matrix}$$

This acid, on treatment with ammonia, whereby Br is exchanged for NH_2, and subsequent hydrolysis, yields *a*-δ-diaminovalerianic acid:

$$C_6H_4\langle\begin{matrix}COOH\\COOH\end{matrix} + H_2N.CH_2.CH_2.CH_2.CH(NH_2).COOH$$

The benzoyl derivative of this diamino acid only differed from Jaffe's ornithuric acid in optical activity; unfortunately, owing to lack of material, the separation of ornithine, as this diamino acid is called, into its stereoisomerides could not be carried out. Sörensen, however, some years later was able to accomplish this, and thus the synthesis of natural ornithine was completed. Ornithine is a product of the hydrolysis of arginine together with urea, and arginine was synthesised by Schulze and Winterstein in 1899 by the addition of cyanamide to ornithine.

By the above series of reactions Fischer prepared *a*-γ-diaminobutyric acid, and the same reactions would lead to the synthesis of lysine, which Fischer and Weigert obtained by a simpler and better method, consisting of the following reactions:

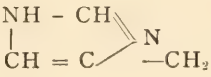
γ-cyanopropylmalonic ester, on treatment with nitrous acid, loses one of its carboxyethyl groups and forms the ethyl ester of α-oximido-δ-cyanovalerianic acid. On reduction with sodium amalgam this compound yields α-ε-diaminocaproic acid, thus:

$$NC.CH_2.CH_2.CH_2.CH\langle^{COOC_2H_5}_{COOC_2H_5} \rightarrow NC.CH_2.CH_2C(:N.OH).COOC_2H_5 \rightarrow$$
$$H_2N.CH_2.CH_2.CH_2.CH(NH_2).COOH$$

This acid has also been synthesised by Sörensen by a very similar method, but its separation into its stereoisomers has not yet been carried out and identity of one of its isomers with natural lysine confirmed.

Fischer and Schlotterbeck have prepared another diaminocaproic acid by heating sorbic acid with ammonia, but its structure has not yet been determined; another diaminovalerianic acid has been obtained from β-vinylacrylic acid.

The other hexone base, histidine, has not been synthesised by Fischer. Its constitution, as suggested by Pauly and proved by Windaus and Knoop, though not yet quite definitely determined, is that of imidazoleaminopropionic acid:

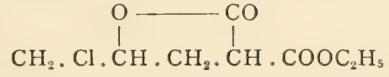


Most probably the amino group is in the α-position, but this still awaits the final proof.

Of the heterocyclic products, proline, as above mentioned, was prepared synthetically by Willstätter.

Two oxypyrrolidine carboxylic acids have recently been obtained by Leuchs in Fischer's laboratory, and deserve mention here in order to complete our knowledge of the amino acids. They were obtained as follows:

γ-chlor-β-oxypropylmalonic ester, prepared from epichlorhydrin and sodium malonic ester, loses alcohol and passes into the ester of δ-chlor-γ-valerolactone-α-carboxylic acid:



This compound on bromination, hydrolysis with concentrated hydrobromic acid and subsequent splitting off of carbonic acid, gives α-brom-δ-chlor-γ-valerolactone, which on treatment

with ammonia gave two oxypyrrolidine carboxylic acids. One of these is probably the inactive form of the optically active oxyproline isolated by Fischer from the products of hydrolysis of gelatine.

Tryptophane was first isolated by Hopkins and Cole and supposed to be either scatoleaminoacetic acid or indoleaminopropionic acid. The work of Ellinger during the last few years points to its having the latter constitution.

The last amino acid which we have to consider is cystine. Our knowledge of this compound rests chiefly upon the work of Mörner and of Friedmann, who showed that on oxidation and loss of carbon dioxide it yielded taurine. Together with Suzuki, Fischer has prepared several of its derivatives and has compared the cystine as obtained from proteins on hydrolysis with that from cystine calculi. Contrary to the statement of Neuberg and Mayer, the two products were found to be identical, and Rothera's work in Cambridge was thus confirmed. At present, therefore, only the one cystine is a decomposition product of proteins, though the isomeric, isocystine, has been synthesised.

Finally, diaminotrioxydodecanic acid, which has only recently been isolated by Fischer and Abderhalden from the products of the hydrolysis of proteins, has not yet been synthesised, and its exact constitution is unknown.

Not only has Fischer synthesised the amino acids, but he has also prepared a large number of derivatives, in addition to the benzoyl and formyl compounds, whereby their isolation, purification, and recognition can be determined. The benzenesulpho derivatives, and especially the β-naphthalene sulpho derivatives, which are obtained by shaking an alkaline solution of the amino acid with the sulphochloride, are very useful for separating amino acids from very dilute or impure solutions. The latter derivative forms compounds with all the amino acids and with many of the polypeptides. It has been used by many workers to isolate amino acids from urine and other secretions (Samuely, Abderhalden and Schittenhelm, Lipstein, Emden and Reese).

The combination of the amino acids with phenylisocyanate in alkaline solution to form phenylureido acids, and the action of hydrochloric acid on these compounds to form their anhydrides, *i.e.* derivatives of hydantoine, first observed by Mouneyrat, has been much used to characterise the amino acids on account of the ease of crystallisation and sharp melting points

of these derivatives. With glycine the following reactions take place:

$$\begin{array}{l} CH_2.COOH \\ | \\ NH_2 \end{array} + C_6H_5.NCO = \begin{array}{l} CH_2.COOH \\ | \\ NH.CO.NH.C_6H_5 \end{array}$$

$$\begin{array}{l} CH_2.COOH \\ | \\ NH.CO.NH.C_6H_5 \end{array} = H_2O + \begin{array}{l} CH_2.CO \\ | \\ NH.CO \end{array} \!\!\rangle N.C_6H_5$$

They are similar in the cases of the other amino acids.

The most important of the derivatives of the amino acids are their esters, which are easily obtained by the action of gaseous hydrochloric acid and methyl or ethyl alcohol. These compounds were first prepared by Curtius, who has used them for his researches upon the aliphatic diazo compounds. As obtained on esterification, the esters are in the form of their hydrochlorides; from these Fischer obtained the free esters by the action of alkali at a low temperature and extraction with ether. The esters are liquids capable of distillation under diminished pressure, and have served as the means of the separation of the amino acids as they result on the hydrolysis of proteins. They have also been of great use in their synthesis.

Many attempts have been made to prepare the acid chlorides of the amino acids, and eventually it was found that they could be prepared by the combined action of phosphorus pentachloride and acetylchloride upon the amino acid. By their means the synthesis of the proteins was materially advanced, as all possible combinations of the amino acids together could be thus made.

II. The Hydrolysis of the Proteins

Of the various methods which have been employed in the study of the composition of the proteins, that of hydrolysis has been made use of most frequently, on account of the better and more certain results which are obtained thereby. The proteins can be hydrolysed by the action of acids, alkalies, and the proteoclastic enzymes; by either of these means a complex mixture of amino acids results. They are of two kinds—the monoamino and the diamino acids. To Drechsel, Hedin, and especially Kossel, we owe an excellent method for the separation of the diamino acids, which lends itself to a quantitative estimation of these compounds as they result on hydrolysis. The

separation and identification of the monoamino acids, on the other hand, by the older methods was extremely crude, and only where a large amount of one or two of the monoamino acids was present, was their isolation and characterisation carried out. Fischer, by introducing the ester method of separating the monoamino acids from one another, has advanced our knowledge of these acids considerably. His method, though not yet quantitative, gives us the means of obtaining about 70 per cent. of the total products.

In the majority of his experiments Fischer used concentrated hydrochloric acid as the hydrolysing agent, in some cases dilute sulphuric acid. This is particularly useful when tyrosine and diaminotrioxydodecanic acid only require isolation, the best results being obtained by boiling the protein for twelve to fifteen hours with five to six times its quantity of 25 per cent. sulphuric acid. This solution, after filtration and dilution with twice its volume of water, is neutralised with baryta, the excess of which is removed with sulphuric acid. The solution, after thoroughly washing out the precipitate of barium sulphate, is concentrated till these acids crystallise out. This method is extremely simple, but requires many days to carry out, as the filtration and washing out of the barium sulphate is very laborious. An improvement has recently been introduced by Abderhalden and Teruuchi, who use hydrochloric acid to hydrolyse the protein; after removal of the greater quantity of hydrochloric acid by evaporation in vacuo, the solution is treated with caustic soda in sufficient amount to exactly combine with the remainder of the hydrochloric acid, when the tyrosine crystallises out.

In all cases where the separation of tyrosine was not required, hydrochloric acid was used as the hydrolysing agent on account of its far greater convenience. The protein is covered with three times its quantity of concentrated hydrochloric acid in a flask; in a short time the majority of the proteins go into solution if the vessel be occasionally shaken, and the hydrolysis is completed by boiling the solution under a reflux condenser for five or six hours. The solution first becomes dark violet in colour and then dark brown; a large proportion of the hydrochloric acid escapes as gas, and a solution remains consisting of the hydrochlorides of the amino acids in 25 per cent. hydrochloric acid. Humin substances and fat-like masses, which separate

out, are filtered off after boiling with charcoal and the hydrochloric acid solution concentrated under reduced pressure. At this stage, if glutamic acid be present in considerable quantities, as in the case of caseinogen, it is separated as hydrochloride. The concentrated solution is therefore saturated with gaseous hydrochloric acid and allowed to stand in a cold place, when crystallisation occurs. The glutamic acid hydrochloride is filtered off, after mixing the solution with an equal volume of ice-cold alcohol; it is purified by dissolving in water, boiling with charcoal and again separating by saturating the solution with gaseous hydrochloric acid.

The next stage consists in the esterification of the amino acids. The acid solution is concentrated as far as possible in vacuo, the residue covered with absolute alcohol, and gaseous hydrochloric acid passed in, till the solution is saturated; it is finally warmed on the water bath. For every kilogram of protein three litres of absolute alcohol are required, as in the process of esterification a large amount of water results, which is harmful to the reaction. In order to complete the esterification the alcoholic solution is concentrated in vacuo to a thick syrup at a temperature not above 50° C., a fresh quantity of absolute alcohol is added, and the liquid again saturated with gaseous hydrochloric acid. This process may be repeated a second time. If glycine be present in the protein in considerable amounts, as in gelatine, it is isolated now as glycine ester hydrochloride. To effect this, a crystal of this compound is added to the solution, and it is allowed to stand for twelve hours at 0° C., when it crystallises out. It is filtered off whilst cold and washed with ice-cold alcohol, and is obtained pure after one recrystallisation from alcohol. A further separation of glycine ester hydrochloride occurs on concentrating the mother liquor, saturating with hydrochloric acid gas, and again allowing to stand. Almost all the glycine can be removed from the mixture in this way. The filtrate contains the ester hydrochlorides of the remaining amino acids, and it is concentrated in vacuo as much as possible at a temperature of 40° C. From this mass the esters are extracted by one of two methods.

The first and older method, which has been the most frequently employed, consists in adding about an equal volume of water and one and a half volumes of ether to the residue, thoroughly cooling in a freezing mixture, and adding strong

caustic soda solution until the free hydrochloric acid is neutralised, then an excess of finally granulated potassium carbonate. For convenience, the residue from a kilogram of protein is divided into four or six portions, which is of great importance in ensuring thorough cooling of the mixture. The esters of aspartic acid and glutamic acid, which are very sensitive to alkali, are thus first separated and dissolved by the ether which is poured off and renewed by adding a fresh quantity. The other esters are then liberated by adding 33 per cent. caustic soda, the whole mass being well shaken with the ether, which is from time to time renewed and replenished by another supply. Finally, sufficient alkali to combine with the whole of the hydrochloric acid and solid potassium carbonate is added, so that a pasty mass is formed, whereby the esters, which are very easily soluble in water, are salted out and extracted by the ether. Throughout the whole process thorough cooling is absolutely essential, and a large amount of ether is required.

The combined ethereal extracts are dried by shaking first with potassium carbonate for ten to fifteen minutes, from which they are poured off, and then for twelve hours with anhydrous sodium sulphate. The ether is distilled off, preferably at the ordinary temperature in vacuo, and a brown oil remains, consisting of the esters of the amino acids.

In the process of extraction a certain quantity of the esters is destroyed by the alkali and therefore not taken up by the ether. The amino acids can be recovered from this by neutralising with hydrochloric acid, filtering off the potassium chloride as it separates on concentration, extracting the residue with alcohol, and repeating the above process of esterification. This may be repeated again, but a certain loss still occurs. To avoid this as far as possible it is preferable to liberate the esters from their hydrochlorides by means of sodium ethylate. This is the second and newer method. The hydrochloric acid is therefore removed as completely as possible by evaporation in vacuo, the residue dissolved in five or six times its quantity of alcohol, and in a small portion of this the amount of chlorine is determined. The calculated amount of sodium dissolved in alcohol to combine with the whole of the chlorine is then added to the thoroughly cooled solution, the sodium chloride formed filtered off, and the alcoholic solution evaporated under greatly diminished pressure. A certain quantity of the lower-boiling

esters pass over into the distillate, but they can be recovered by acidifying with hydrochloric acid and evaporating, when they are obtained as amino acid hydrochlorides. The dark brown residue which remains in the distilling flask is fractionally distilled in vacuo, leaving a mass consisting of tyrosine and other amino acids, which in the first method are contained in the mass of potassium carbonate.

The distillation in vacuo is carried out first at the pressure of 10–12 mm. produced by the water pump, and then at a pressure of 0·5 mm. produced by a Geryck pump. At 10–12 mm., three fractions (up to 60°, 80°, 100°) are collected, the temperature taken being that of the water bath; the distillation is then continued at 0·5 mm., the first fraction being that at the temperature of the boiling water bath; several fractions are then collected up to 160°, the temperature being procured by the use of an oil bath. The residue, which does not distil at this temperature, consists of a dark brown oil; it sets to a hard mass on cooling, and contains, amongst other substances, leucinimide.

The various fractions, so obtained, consist of a mixture of the esters of two or more amino acids, and they are again fractionated in vacuo; this is not essential for the fractions distilling above 100° C. at 0·5 mm. pressure, which contain the esters of phenylalanine, aspartic acid, glutamic acid, and serine. These esters are separated by taking advantage of their different solubilities in water, ether, petroleum ether; *e.g.* phenylalanine ester is soluble with difficulty in water, and is extracted from the aqueous solution of the esters with ether, the esters of aspartic and glutamic acids remaining in the water. Serine ester is insoluble in petroleum ether; on mixing the fraction containing it with petroleum ether it separates as an oil, the esters of the three other acids remaining in solution.

Finally the esters must be converted into the amino acids; in the case of the lower-boiling fractions, they are hydrolysed by boiling with water under a reflux condenser for five to six hours until the alkaline reaction disappears; leucine may crystallise out during this process. The esters in the higher-boiling fractions which contain glutamic and aspartic acids are hydrolysed by boiling with baryta; if hydrolysed by water, they remain as acid esters. On cooling, aspartic acid may separate as the barium salt of the racemised acid. The

phenylalanine ester fraction is hydrolysed by evaporating with concentrated hydrochloric acid, when the hydrochloride is obtained.

The ester method can be combined with the methods for obtaining tyrosine and the diamino acids. The protein is therefore hydrolysed by sulphuric acid, the tyrosine separated by crystallisation, and the diamino acids precipitated by phosphotungstic acid. The filtrate, after removal of phosphotungstic acid, is treated as above described for the separation of the monoamino acids.

From the above it is obvious that a mixture of amino acids is still present; their final separation, as they result from the various fractions, has still to be carried out. The methods employed are best described by taking a particular protein as illustration, *e.g.* crystallised oxyhæmoglobin, which was hydrolysed by Abderhalden by the above method, and gave five fractions of esters from which the appended weights of amino acids were isolated:

Temperature.	Pressure.	Weight of Ester.	Weights of Amino Acids.
Fraction I. To 40° (vapour)	10 mm.	64·2 gm.	14·2 gm. alanine.
„ II. 40—60° „	10 „	107·0 „	26·0 gm. alanine, 30·7 leucine, 1 gm. protein.
„ III. 100° (water bath)	0·2 „	403·4 „	247·5 gm. leucine, 21.5 gm. protein.
„ IV. 100—130° (oil bath)	0·2 „	81·7 „	19·5 gm. phenylalanine, 11·3 gm. aspartic acid, 4·2 gm. glutamic acid, 1·7 gm. serine.
„ V. 130—160° „	0·2 „	93·0 „	21·1 gm. phenylalanine, 4·1 gm. glutamic acid, 11·0 gm. aspartic acid, 1·0 gm. serine.

Oxyhæmoglobin contains no glycine, so that its separation was not necessary, but as ester hydrochloride four-fifths can be isolated when the protein contains 20 per cent. in its molecule; the remainder is distilled as ester, and passes into the first fraction with alanine ester, from which it is separated by conversion into its ester hydrochloride. The alanine is then separated by crystallisation, after removal of the hydrochloric acid, and is characterised by conversion into its benzoyl derivative. Owing to partial racemisation occurring during the

processes of hydrolysis and esterification, its rotation is generally found too low, and the melting-point of its benzoyl derivative is not quite sharp.

The presence of valine, or *a*-aminoisovalerianic acid, is not mentioned in this paper. Its separation from leucine, with which it is generally present, is carried out with difficulty, and depends on the fractional crystallisation of the free acids and their copper salts.

Leucine, again, as it results on hydrolysis, is partially racemised. Its characterisation is therefore more difficult, but this is carried out by completing the racemisation by heating it with baryta at 170–175° C. for twenty-four hours, and then converting it into its hydantoin derivative. Isoleucine is probably mixed with leucine, but no special separation of this isomer was performed by Fischer.

Proline is the only amino acid which is easily soluble in absolute alcohol. By evaporating the mixture in which it is contained to dryness and extracting with absolute alcohol, it can be easily isolated. This compound, when obtained by hydrolysis, also exists in the racemic and optically active forms; by conversion into the copper salt the two varieties can be separated by alcohol in which the copper salt of the active form is soluble. The racemic acid is characterised by a determination of the amount of water and the content in copper of its copper salt, the active acid by its hydantoin derivative.

Phenylalanine is so easily isolated as ester that an analysis of its hydrochloride, obtained by evaporating the ester to dryness with hydrochloric acid, is sufficient for its identification. Small quantities can be identified by oxidation to phenylacetaldehyde, which has a very distinctive smell.

Serine, on account of the insolubility of its ester in petroleum ether, generally requires no great amount of work to characterise it. After hydrolysis by baryta, the solution is concentrated when it crystallises out, and elementary analysis determines its nature. The *β*-naphthalene sulpho-compound may be used, if further characterisation be necessary.

Aspartic and glutamic acids are separated partially after the hydrolysis of their esters by baryta, when the barium salt of dl-aspartic acid crystallises out on cooling. A further quantity may be isolated by crystallisation of the free acid, but the

remainder is only obtained after the removal of the glutamic acid as hydrochloride.

The ester method has not led to the discovery of a large number of new amino acids; to this category proline and oxyproline belong. The possibility that proline is a secondary product formed by the action of acid on another amino acid is negatived by the fact that it results when the proteins are hydrolysed by alkali. The great use of the ester method has been to separate the amino acids, and to determine their great variety in all the proteins; formerly, only those existing in large amounts, such as tyrosine, leucine, aspartic acid, were isolated. The ester method also gives larger amounts. Alanine, serine, and phenylalanine, which was only once isolated by Schulze from plant proteins, were seldom found, but now their universal presence in all proteins is definitely established. Phenylalanine, in its distribution, is the chief aromatic compound, since tyrosine does not occur in all proteins, and it often exceeds in amount that of tyrosine when both exist in the same protein.

These results can be seen at a glance by referring to the following table, which also shows the various amounts of individual amino acids in percentages, as they result on the hydrolysis of proteins:

	Globin from oxyhæmoglobin.	Caseinogen.	Gelatine.	Silk fibrin.	Egg-albumin.
Glycine . . .	...	...	16·5	36·0	...
Alanine . . .	4·2	0·9	0·8	21·0	2·1
Valine . . .	present	1·0	1·0	...	...
Leucine . . .	29·0	10·5	2·1	1·5	6·1
Proline . . .	2·3	3·1	5·2	present	2·2
Phenylalanine .	4·2	3·2	0·4	1·5	4·4
Glutamic acid .	1·7	11·0	0·9	...	8·0
Aspartic acid . .	4·4	1·2	0·6	present	1·5
Cystine . . .	0·3	0·06	...	...	0·2
Serine . . .	0·6	0·23	0·4	1·6	...
Tyrosine . .	1·5	4·5	...	10·5	1·1
Lysine . . .	4·3	5·8	2·7	present	...
Arginine . .	5·4	4·8	7·6	1·0	...
Histidine . .	11·0	2·6	0·4	present	...
Oxyproline . .	...	...	3·0	...	...
Tryptophane . .	...	...	...	...	present

Not only has Fischer hydrolysed proteins by acids and by alkali, but also by the enzymes pepsin and trypsin. The latter gives essentially the same products as acids, but its action is

not complete. Even on prolonged action, when the biuret reaction is absent or only very faint, a complex product together with amino acids results. This complex polypeptide, as it is termed, contains the whole of the proline and phenylalanine contained in the protein, together with other amino acids. It is apparently not identical with Kühne's antipeptone which gave the biuret reaction. On complete hydrolysis by acid, it yielded the same quantity of proline and phenylalanine as would result from the protein by acid hydrolysis.

In the animal body the action of trypsin is preceded by that of pepsin. If a protein be first digested by pepsin and then by trypsin, the same complex polypeptide might be expected to result, but this was not the case. It was less in amount, and did not contain the whole amount of the proline and phenylalanine of the protein, a certain portion of these being found with the other amino acids, which had been split off. It would thus appear as if the protein molecule contained a special nucleus, as suggested by Kossel, who believes that it consists mainly of the diamino acids; these make up 90 per cent. of the protamine molecule, the protein molecule containing less of this nucleus and more monoamino acids than the protamine. Histones are a transition product between the protein and protamine. Unfortunately, by the method adopted by Fischer, a nucleus consisting mainly of diamino acids could not be definitely determined, since the phosphotungstic acid used not only precipitated the complex polypeptide, but also the diamino acids, so that it was impossible to tell whether they were free or combined together in this polypeptide. Subsequent work, if attended with such far-reaching results, will certainly decide this question, especially as less complex combinations of amino acids have already been isolated from proteins. New amino acids and oxyamino acids may still be discovered; Skraup's results point to the existence of two more diamino acids and other oxy-amino acids; their exact constitution is still very uncertain. His work cannot be further mentioned here.

The hydrolysis of various proteins has been carried out by Abderhalden and several co-workers in the hope of being able to obtain closer relationships between the members of the various classes of proteins, and more distinctions between the classes. Abderhalden's book on physiological chemistry brings out these points as well as many others of great interest.

III. The Synthesis of the Proteins. The Polypeptides

Many theories have been advanced concerning the constitution of the proteins as to how the amino acids, the key-stones, are combined together. The majority of the views regard the amino acids as being bound together in an anhydride-like manner in the form of acid amides. This view has been very strongly supported by Hofmeister, and several experimenters had already attempted to combine the amino acids together in this manner. Thus, Schaal made the anhydride of aspartic acid, which was further condensed by Grimaux and Schiff. Schutzenberger condensed amino acids with urea, Lilienfeld employed a mixture of amino acid esters, and Balbiano and Frasciatta obtained a horny mass, an anhydride of glycine.

Not, however, until Fischer commenced his systematic researches upon the combination of the amino acids with one another in 1901 was any real progress made. Since then the enormous number and variety of products which have been prepared by Fischer and his pupils have given us an actual knowledge as to how the proteins are built up, and they show us how much more complicated the proteins are than the fats and carbohydrates, the other natural constituents of animal and vegetable cells. The combinations of the amino acids have been called by Fischer polypeptides, those containing two, three, four, etc., acids being di-, tri-, tetra-peptides, etc. They remind us in their nomenclature of monosaccharides, dissacharides, polysaccharides, and of peptone, which Fischer regards as a mixture of polypeptides.

It was found by Curtius and Goebel many years ago that the ethyl ester of glycine, when dissolved in water, lost two molecules of alcohol, and was converted into diketopiperazine, or, as it is now better called, glycine anhydride,

$$\begin{array}{l} NH\,.\,CH_2\,.\,CO \\ \quad\quad\quad\quad\quad\quad | \\ CO\,.\,CH_2\,.\,NH \end{array}$$

This substance formed the starting-point of E. Fischer's investigations; by boiling it with concentrated hydrochloric acid the piperazine ring was split, and it gave the hydrochloride of the base $C_4H_8N_2O_3$, thus

$$\begin{array}{l} NH\,.\,CH_2\,.\,CO \\ \quad\quad\quad\quad\quad\quad | \\ CO\,.\,CH_2\,.\,NH \end{array} + H_2O = H_2N\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,COOH$$

This compound is glycylglycine, as termed by Fischer, the group $NH_2.CH_2.CO$ being called the glycyl group. It might be mentioned that the benzoyl derivative of this compound was obtained by Curtius in 1882.

The ester of this compound was formed when the glycine anhydride was boiled with alcoholic hydrochloric acid. Both free acid and the ester have a great tendency to change back into the anhydride, a property which has been utilised in isolating such compounds from the products of hydrolysis of proteins. The amino group is also very reactive, *e.g.* with chlorcarbonic acid ester it gives carbethoxyglycylglycinester, from which, on hydrolysis, glycylglycinecarboxylic acid is obtained. When heated with leucinester, carbethoxyglycylglycinester undergoes a similar condensation, forming carbethoxyglycylglycylleucine, where three molecules of amino acids are coupled together.

The diketopiperazine of alanine, and that of leucine, the so-called leucinimide, both gave the corresponding dipeptides alanylalanine and leucylleucine,

$$H_2N.CH(C_4H_9).CO.NH.CH(C_4H_9).COOH.$$

Difficulties were, however, experienced with the condensation of the other amino acid esters, and with the more complex esters of the dipeptides, as also with the condensation of dissimilar amino acids, where several products may result, so that progress by these means became almost impossible. The compounds so prepared, as expected from their constitution, gave the red biuret reaction, which was shown by Schiff to be given by compounds having $CO-NH$ groups joined together directly, or by a C atom or by a N atom.

About this time (1902) Curtius and Benrath prepared benzoylpentaglycinaminoacetic acid, and two years later Curtius showed that his biuret base was triglycylglycinester. This compound is the ester of Fischer's triglycylglycine. Triglycylglycinester, according to Curtius and Gumlich, changes into an anhydride, which is an octapeptide.

The method of preparing dipeptides from the diketopiperazines a few years later again proved useful, when it was found that by heating the esters of the amino acids to 150–180° combination occurred, and instead of splitting open the ring by boiling with concentrated hydrochloric acid, dilute alkali at the ordinary

temperature produced the same result in fifteen to twenty minutes. The diketopiperazines of alanine, leucine, phenylalanine, tyrosine are thus easily prepared, as also the corresponding dipeptide. As yet the dipeptides of the diamino acids, lysyllysine and histidylhistidine and serylserine, have only been obtained by this method by Fischer and Suzuki; in these cases the methyl ester of the amino acid was more easily converted into the diketopiperazine. The method does not lend itself to the preparation of mixed diketopiperazines. These are obtained by the action of ammonia on the *a*-halogenacyl derivative of the amino acid ester, *e.g.* glycylalanine anhydride,

$$Cl.CH_2.CO.NH.CH(CH_3).COOC_2H_5 + 2NH_3 = NH_4Cl + C_2H_5OH + NH\begin{<}{l}CH_2.CO\\CO.CH.CH_3\end{>}NH$$

The simple method of combining the acid chloride of an amino acid with another amino acid for the synthesis of polypeptides could not be employed, as these derivatives were unknown and impossible to prepare. The carbethoxy derivative, however, of the amino acid, or polypeptide, when warmed with thionylchloride, was found to give the acid chloride, and this compound reacted with the esters of amino acids or polypeptides to form the carbethoxy derivates of polypeptides, thus carbethoxyglycylglycine on treatment with thionylchloride yielded the acid chloride which reacted with glycylglycinester to form the carbethoxy derivative of triglycylglycinester. The conversion of this compound into the true tetrapeptide, owing to the firm union of the COOH group, was not possible, and a third method, which reminds us of the preparation of the amino acids, was attempted, and proved most fruitful.

This method consists in introducing an *a*-halogenacyl residue into the molecule of an amino acid or polypeptide, and then treating this compound with ammonia, whereby the Cl is exchanged for NH_2; thus chloracetyl tyrosine, obtained from chloracetyl chloride and tyrosine, on treatment with ammonia gives glycyltyrosine,

$$CH_2Cl.COCl + HOOC.CH(NH_2).CH_2.C_6H_4OH = HCl + HOOC.CH(NH.CO.CH_2Cl).CH_2.C_6H_4OH$$
$$.HOOC.CH(NH.CO.CH_2Cl).CH_2.C_6H_4OH + NH_3 = HCl + HOOC.CH(NH.CO.CH_2.NH_2).CH_2.C_6H_4OH$$

and chloracetylglycylglycinester gives diglycylglycinester, from which on hydrolysis the free acid is obtained.

In just the same way the alanyl and leucyl radicles can be introduced by using *a*-brompropionylbromide and *a*-bromisocapronylchloride. Leucylproline can be obtained in this manner, the *a*-pyrrolidine carboxylic acid also lending itself to synthesis by this reaction. The residue—prolyl—can be introduced by combining amino acids with the chloride of *a*-δ-dibromvalerianic acid; the compound obtained on treatment with ammonia, just as in the synthesis of *a*-pyrrolidine carboxylic acid, after exchanging the Br atoms for NH_2, loses ammonia, forming the prolyl dipeptide, *e.g.* prolylalanine. Not only can the simple monoamino acids be combined by this method, but also cystine, from which, *e.g.*, dialanylcystine results. The aspartic acid radicle is introduced by means of fumarylchloride; when combined with alanine, fumaryldialanine is formed; this adds on ammonia, yielding asparagyldialanine. Lastly, the phenylalanine residue can be attached by means of phenylbrompropionyl chloride.

A large number of mixed dipeptides, and also of tri-, tetra-, etc., peptides, have been prepared by this method, which, however, only admits of the lengthening of the chain in one direction —namely, on the side of the amino group.

It was of extreme importance to be able to lengthen the chain upon the side of the carboxyl group, and this is possible only by means of the acid chloride. As previously stated, the acid chlorides of the amino acids and polypeptides were not known, but that the acid chloride of the carbethoxy derivative was prepared by the action of thionylchloride upon it. The presence of the halogenacyl radicle in the amino acid, such as bromcapronyl, again allows of the formation of the acid chloride of the amino acid or polypeptide, and this compound reacts with the esters of other amino acids in the following way:

$$C_4H_9 . CHBr . CO . NH . CH_2 . COCl + 2NH_2 . CH_2 . COOC_2H_5$$
$$= HCl . NH_2 . CH_2 . COOC_2H_5 +$$
$$C_4H_9 . CHBr . CO . NH . CH_2 . CO . NH . CH_2 . COOC_2H_5$$

Subsequent hydrolysis of the ester and treatment with ammonia gives the polypeptide. This process can be carried out indefinitely by again making the acid chloride of the new compound and condensing it with an amino acid or a polypeptide. Any conceivable combination can be prepared by

this method, *e.g.* leucylalanine, alanylleucine, alanylleucylglycine, leucylalanylglycine, glycylalanylleucine, etc.

Fischer has ultimately been able to prepare the acid chloride of the amino acid so that it can be used directly for synthesis. Whereas the acid chlorides of the halogenacyl derivatives were easily prepared by the action of phosphorus chloride, this did not take place with hippuric acid. After many attempts to prepare hippuryl chloride, success at length was attained when hippuric acid was heated with acetylchloride and phosphorus pentachloride together. By simply extending this method of preparation to the amino acids themselves, *i.e.* by shaking them in a finely powdered condition with acetylchloride and phosphorus pentachloride, Fischer obtained the acid chlorides of the amino acids, whereby a step in the synthetical processes can be saved.

During the course of the last year several higher polypeptides have been synthesised by these methods; these are two hexapeptides, a heptapeptide, an octapeptide, and even a dodekapeptide. They all consist principally of glycine residues, the dodekapeptide having one leucine and eleven glycine radicles. Such long glycine chains probably do not exist in the protein molecule, except possibly in gelatine, which contains about 20 per cent. glycine. Their study, however, is of great importance in that they cannot exist in stereoisomeric forms, and the knowledge of their properties may lead to the isolation of a higher polypeptide from the proteins themselves. Further, the material is of easy access, glycine being readily prepared synthetically, which is not the case with the other amino acids, many of which are more easily obtained by the hydrolysis of proteins than by synthesis.

In a quite recent paper Fischer gives an account of the preparation of an octadecapeptide, built up of fifteen glycine and three l-leucine residues, *i.e.* a polypeptide containing six more members in its molecule than the above-mentioned dodekapeptide. Its preparation is of great interest, as it shows very clearly how the synthetical method has been employed in these researches. Pentaglycylglycine and d-*a*-bromisocapronyldiglycylglycine, $BrCH(C_4H_9)CO.[NHCH_2CO]_2.NHCH_2COOH$ are used. The acid chloride of the latter compound is first prepared and combined with the hexapeptide. The bromo compound so obtained on treatment with liquid ammonia gives l-leucyl-

octaglycylglycine. This decapeptide, on combination with bromisocapronyl diglycylglycine, and subsequent replacement of Br by NH_2, yields the tetradecapeptide

$$NH_2CH(C_4H_9)CO.[NHCH_2CO]_3.NHCH(C_4H_9)CO.[NHCH_2CO]_8.NHCH_2COOH,$$

and a repetition of the process of combining with bromisocapronyldiglycylglycine gives the octadecapeptide

$$NH_2CH(C_4H_9)CO.[NHCH_2CO]_3.NHCH(C_4H_9)CO.[NHCH_2CO]_3.NHCH(C_4H_9)CO.[NHCH_2CO]_8.NHCH_2COOH.$$

Many technical difficulties had to be surmounted in its preparation which were successfully overcome; *e.g.* prevention of frothing by shaking up with glass beads, etc.

The molecular weight of this compound is 1213. It far exceeds that of the fats, of which tristearin has the molecular weight 891, and it belongs to the most complicated combinations ever obtained synthetically without our losing the knowledge of its constitution. If, in place of the glycine residues, it contained tyrosine, phenylalanine, or leucine residues, its molecular weight would be increased two- to three-fold, *i.e.* to values taken as the normal for many natural proteins. The values of 12,000—15,000 for other proteins, according to Fischer, are uncertain, as we have no guarantee of the purity of these natural substances.

Up to the present time nearly one hundred different polypeptides have been prepared. Their structure is derived directly from their synthesis, and they are generally represented as in the formulæ given in the above equations. Other structures are also possible; indications of these have been observed in their study, and they are at present only of theoretical interest.

The configuration of the polypeptides is of extreme importance, for, with the exception of glycine, all the amino acids contain an asymmetric carbon atom. According to van't Hoff's formula, 2^n, the number of isomers possible when two amino acids are combined together is four, namely, the dd, ll, dl, ld forms; and two racemic forms—dd, ll and dl, ld—can be obtained from these. With more amino acids coupled together the complications are still greater, and their separation well-nigh impossible. Fortunately, these conditions do not seem to be present in the protein molecule, since the amino acids as they result on hydrolysis are optically active and hence exist in

only one form. Optically active polypeptides, in addition to glycyl-l-tyrosine and leucyl-l-tyrosine, have quite recently been prepared by Fischer. These are l-leucylglycine, l-leucyl-d-alanine, l-leucyl-l-leucine, and they are composed of the stereoisomers obtained from the proteins. Glycyl-d-alanine, d-alanyl-d-alanine, and d-alanyl-l-leucine have since been synthesised. Their synthesis is far more tedious, since it necessitates the preparation of the optically active forms. In their preparation the acid chloride method has been used, and a curious change from the dextro to the lævo form, termed Walden's rearrangement, has been observed by Fischer, thus d-leucine is converted into isobromcaproic acid chloride; this when combined with l-leucine and treated with ammonia gives l-leucyl-l-leucine, instead of the expected d-leucyl-l-leucine.

The material employed in the preparation of nearly all the polypeptides consisted of the racemic amino acids, from which two racemic compounds would be expected to result. These first appear in the halogen intermediate compounds,

$$\mathrm{Br.\mathbf{C}.HR.CO.NH.\mathbf{C}HR.COOH}$$[1]

and a separation in a few cases has been effected at this stage. In other cases both the dipeptides have been isolated after their formation. In the majority of cases, however, only one product has been obtained; this may either consist of mixed crystals of the two forms, or only the one form may have resulted. Instances of this kind have been noticed in other classes of compounds, and it can only be assumed that in the synthesis one arrangement is more favourable than the other, and therefore appears in much larger amount under the influence of asymmetry, or the velocity of the reaction between one pair is greater than between the other pair. The influence of asymmetry is well known to play a great part in the rate of reactions, as exemplified in the action of enzymes. Both forms may also be present, but the one in greater quantity than the other.

The nomenclature of the polypeptides in the case of those consisting of optically active amino acids is quite simple, *e.g.* d-leucyl-l-alanine, but where the racemic forms are concerned it is more difficult. The examples, dl-leucylglycine and glycyl-dl-leucine, designate the two isomeric inactive dipeptides, containing only one asymmetric carbon atom. The two racemic dipeptides

[1] The asymmetric carbon atoms are in thicker type.

with more than one asymmetric carbon atom are represented as follows:

d-alanyl-d-leucine l-alanyl-l-leucine	I.	d-alanyl-l-leucine l-alanyl-d-leucine	II.

but as their configuration must be first established, Fischer has simply labelled them A and B, the A denoting the more insoluble. The synthesis of the optically active forms and their combination together would definitely decide the constitution, but a simpler method has been found by studying the action of trypsin upon them. The A combination was hydrolysed; d-alanyl-l-leucine contains the natural amino acids, and hence the form II. most probably corresponds to the more insoluble racemic dipeptide.

The configuration of the diketopiperazines is far more complex and need not be entered into here.

Although the amino acids are in all probability joined together in the manner of acid amides, it is possible that other couplings may also be present in the protein molecule. Ethers of the oxyamino acids, their esters with other amino acids are conceivable; and polyoxyamino acids, if present, suggest a still more complex combination. The presence of diketopiperazine rings is also likely, as they are so easily converted by alkali into the dipeptides; a change of this kind may take place in the formation of the so-called albuminates and on coagulation. The hydrolysis of the polypeptides by the proteolytic enzymes, and their giving of the red biuret reaction like peptone, point most strongly to the acid amide manner of combination of the amino acids in the protein molecule.

IV. The Action of Enzymes upon the Polypeptides

We have seen that, by synthesis, a very large number of polypeptides have been prepared from the amino acids; their number is almost infinite, even if only the optically active forms, as they occur in nature, be coupled together. Some light might be shed upon what combinations actually occur in the protein molecule by the study of the products of hydrolysis, when this is not carried to the ultimate stage. Such intermediate products are already known and designated proteoses and peptones. They consist of mixtures of complex polypeptides, and at present our methods are not sufficiently perfect for separating polypeptides from one another and from amino acids. They

result when the proteins are hydrolysed by the proteolytic enzymes, pepsin, and trypsin. Even under identical conditions it is difficult to determine how far hydrolysis has proceeded under their influence, as two preparations are scarcely ever of the same strength. Hydrolysis by acids and alkalies is not so limited, as they tend to give the ultimate end products which at the same time undergo partial racemisation.

The study of the behaviour of the synthetical polypeptides to trypsin throws much more light upon the combinations which may actually occur in the protein molecule. Each protein may again possess different combinations; their properties, as also the various amounts of the same amino acid, obtained by hydrolysis, point to a variety of combinations.

Fischer commenced his investigations upon this subject in conjunction with Bergell at a time when only a few of the dipeptides had been prepared. The hydrolysis of these by trypsin was found to depend upon various factors. Further and much more complete investigations were carried out with Abderhalden, as the result of which the synthetical polypeptides could be divided into two classes:

Those Hydrolysed	*Those not Hydrolysed*
*alanylglycine	glycylalanine
*alanylalanine	glyclyglycine
*alanylleucine A	alanylleucine B
*leucylisoserine A	leucylalanine
glycyl-l-tyrosine	leucylglycine
leucyl-l-tyrosine	leucylleucine
*alanylglycylglycine	aminobutyrylglycine
*leucylglycylglycine	aminobutyryl-aminobutyric acid A
*glycylleucylalanine	aminobutyryl-aminobutyric acid B
*alanylleucylglycine	aminoisovaleryl-glycine
dialanylcystine	glycylphenylalanine
dileucylcystine	leucylproline
tetraglycylglycine	diglycylglycine
triglycylglycinester (Curtius' biuret base)	triglycylglycine
	dileucylglycylglycine

The two classes show firstly the endless variety of the simple polypeptides, and secondly, on closer examination, that

* These are racemic compounds.

their hydrolysis by trypsin depends upon several factors. The influence of their structure is exemplified by alanylglycine which is hydrolysed, the isomeric glycylalanine not being hydrolysed. Similarly, alanylleucine A is acted upon, but not leucylalanine. The influence of the individual amino acid is more marked; thus, where alanyl is the acyl radicle, hydrolysis takes place; but not when leucyl or aminoisovaleryl (valyl) are in this position. Hydrolysis also occurs when tyrosine, serine, and cystine stand at the end of the chain.

The configuration of the molecule is also of importance; the racemic compounds are hydrolysed asymmetrically with the formation of the optically active amino acid which occurs in the proteins; thus alanylleucylglycine gave d-alanine and leucylglycine mixed with the other form originally contained in the racemic tripeptide. The identification of the racemic form in the case of the combinations of alanine and leucine by means of trypsin has been previously mentioned. Alanylleucine A was partially hydrolysed, and was supposed to be composed of the naturally occurring amino acids. This has quite recently been proved by the study of the action of trypsin upon polypeptides built up entirely of optically active amino acids. Again, leucylleucine was not attacked, and it is now shown that it is the racemic compound, l-leucyl-d-leucine and d-leucyl-l-leucine.

The following list gives these recent results:

Those Hydrolysed	*Those not Hydrolysed*
d-alanyl-d-alanine	d-alanyl-l-alanine
d-alanyl-l-leucine	l-alanyl-d-alanine
l-leucyl-l-leucine	l-leucyl-glycine
l-leucyl-d-glutamic acid	l-leucyl-d-leucine
	d-leucyl-l-leucine.

The number of amino acids in the molecule, *i.e.* the length of the chain, is very interesting in the case of the glycine polypeptides. Not until five glycine radicles, as in tetraglycylglycine, are present, is hydrolysis produced by trypsin. It is curious to note that the ester of triglycylglycine is hydrolysed, but not the free acid. This is the biuret base of Curtius, and was previously examined by Schwarzschild in its behaviour to trypsin. It is probable that the configuration of the dileucyl group in dileucylglycylglycine prevents its hydrolysis by trypsin,

as leucylglycylglycine is acted upon, though not leucylglycine. None of these polypeptides was hydrolysed by pepsin. In all probability the chain is not sufficiently long, and it would be interesting to know the result of the action of pepsin upon the recently prepared octapeptide and dodekapeptide.

The results undoubtedly show which combinations are most likely to occur in the protein, and they are of great importance for their synthesis, as only those polypeptides containing optically active amino acids combined together in the way that trypsin acts upon them need be prepared.

In the earlier experiments, an extract of dried pancreas was employed as the hydrolytic agent, but in the later experiments pure pancreatic juice, obtained from a pancreatic fistula by Pawlow, was used. There was a striking difference in their behaviour to certain dipeptides—namely, leucylalanine, leucylglycine, leucylleucine. These were not hydrolysed by the pure juice, but by the extract of dried pancreas, which would contain the autolytic enzyme as well as the enzyme trypsin, they were hydrolysed.

These differences of enzymes to polypeptides may show differences in the pancreatic juice of various animals; it is well known that some animals are able to digest substances left untouched by others, and further, that though not hydrolysed by trypsin, they may be attacked and converted into amino acids by the enzymes of other organs such as the liver, spleen, etc., and thus made assimilable by the animal organism.

Investigations as to whether the various polypeptides are hydrolysed by the organism have been made by Abderhalden and several co-workers, by injecting them and ascertaining whether they were excreted as such or as their constituent amino acids in the urine. These products were not found in the urine, and it is concluded that they are utilised in the same way by the organism as the proteins themselves are in metabolism, *i.e.* they are split up and their nitrogen excreted as urea. In fact, not only were the optically active compounds utilised, but also the racemic compounds. Slight differences were noticed between dogs and rabbits which did not entirely hydrolyse the racemic products, *e.g.* dl-leucylglycine. The anhydride of leucylglycine and glycocoll were found in the urine when somewhat large quantities were injected.

The synthetical polypeptides have also been employed by

Abderhalden to determine the nature of the proteolytic ferments in the various organs, whether they contain a single enzyme or a mixture. Commercial trypsin, or a dried extract of the pancreatic gland, has already been seen to act differently from pure pancreatic juice, and the same applies to pure gastric juice and commercial pepsin. Glycyl-l-tyrosine is a very convenient substance to distinguish between pepsin and trypsin, as it is not split by the former, but hydrolysed by the latter to glycine and tyrosine. By its means duodenal juice has been shown to contain a ferment like pepsin, since it was not hydrolysed. The ferments of the liver, muscle, kidney contained in the juice obtained by Buchner's method of grinding with sand, mixing with kieselguhr and pressing out at 300 kilograms pressure, behaved like trypsin, but were more active, as they hydrolysed dl-leucylglycine, glycylglycine, glycylalanine, etc. They are therefore less selective in their action, and consequently polypeptides contained in peptone absorbed from the intestine may yet be hydrolysed and assimilated by the various organs. The resultant action of trypsin upon proteins is the production of amino acids and a complex polypeptide (antipeptone of Kühne). This polypeptide, on absorption, will be broken down and be assimilated by the different organs.

The resistant polypeptide may contain other kinds of combination, such as ether, ester (Warburg has found, however, that trypsin acts upon leucinester), diketopiperazine, which are not broken open by trypsin or pancreatic juice, but by the ferments of the liver. The action of arginase upon arginine, a combination of ornithine and urea, which is not acted upon by trypsin, as also the changes which the purine bases undergo in the liver by special enzymes are examples of this kind. In the animal body, the combined action of ferments plays a great part. The resistant polypeptide does not appear in quite the same form when the protein is acted upon first by pepsin and then by trypsin. According to Cohnheim hydrolysis by pepsin followed by erepsin, the ferment obtained from the mucous membrane of the duodenum, produces the same result as pepsin followed by trypsin. This ferment has been shown by Abderhalden to hydrolyse polypeptides not acted upon by trypsin.

It would seem, therefore, as if the study of the action of pancreatic juice would not lead directly to the exact manner of combination in the protein molecule, but it will, nevertheless,

give us a very good insight as to a very large number of these combinations. The only way to arrive at the ultimate solution is the isolation of various complexes before complete hydrolysis. Pick and Zunz have separated various proteoses and peptones, but these are still too complex, as also are the bodies, called kyrines, prepared by Siegfried. We must determine the combinations of two, of three, of four, as they exist, and their possible combinations with each other. A commencement has already been made by Fischer and Abderhalden, who have isolated three dipeptides.

A great deal of confusion has for a long time existed concerning the nature of the proteolytic ferments contained in germinating seeds and various plants. By investigating the action of these enzymes upon various polypeptides, Abderhalden and Schittenhelm found the enzymes of the germinating seeds of wheat and lupines contained a tryptic ferment; and Abderhalden and Teruuchi showed that the endotryptase of yeast and pepsin were like trypsin in their action, whereas the juice of *Nepenthes* contained an enzyme like pepsin in its nature.

V. The Isolation of Polypeptides from Proteins

In 1902 Fischer described the results of some experiments which he had made in conjunction with Bergell upon the isolation of a dipeptide from silk by means of the combined action of acid, alkali, and trypsin. By the action of hydrochloric acid upon silk fibrin, a peptone is obtained which gives a marked reaction for tyrosine. If this be treated with trypsin, the tyrosine is completely split off, and another peptone free from tyrosine results, which when acted upon by baryta, loses ammonia and yields a dipeptide. This dipeptide was considered to be glycylalanine, though the proof could not be satisfactorily given at the time.

This product was not again obtained until quite recently, as the exact conditions of its formation could not be repeated; Fischer and Abderhalden then isolated it in the form of its diketopiperazine. The silk fibrin was acted upon either by sulphuric acid followed by trypsin or by hydrochloric acid; the product was esterified and distilled in the ordinary manner at a low temperature, whereby the esters of the monoamino

acids are removed and the residue treated with ammonia. A substance crystallised out, which was found to be identical with the diketopiperazine formed from glycine and alanine. On hydrolysis it yielded glycine and d-alanine, but whether it was glycyl-d-alanine or d-alanylglycine could not be exactly determined, but most likely it is the anhydride of glycyl-d-alanine, as the product is not hydrolysed by trypsin.

At the same time another dipeptide, glycyl-l-tyrosine, was mentioned, but its constitution was only determined later. Its anhydride has been found to be identical with the synthetical glycyl-l-tyrosine anhydride, and it occurred mixed with the glycyl-d-alanine anhydride obtained in the above manner. Glycine and l-tyrosine resulted on hydrolysis.

By the same method, the anhydride of glycine and leucine has been prepared from elastin; it corresponded exactly to glycyl-l-leucine anhydride. To these three dipeptides, a fourth must be added. It is described by Levene and Beatty as prolylglycine anhydride and was obtained from gelatine.

Further, a crystalline substance, probably a dipeptide, which gives proline and phenylalanine on hydrolysis, has been isolated from the products of the acid hydrolysis of gliadin by Osborne and Clapp.

The protones, which are obtained from the protamines by digestion, have a molecular weight of about 420. Just as in the protamines, eight-ninths of their nitrogen is in the form of arginine. Kossel therefore believes that they are mixtures of tripeptides, such as diarginylalanine, diarginylserine, etc., which have the molecular weights of 401 and 417 respectively.

Leucinimide, leucylleucine anhydride, described many years ago by Bopp, has not yet again been isolated, and, according to Fischer, its existence is doubtful.

The work of Emil Fischer emphasises most strongly the importance of the knowledge of organic chemistry to physiological chemistry, in which branch the proteins are generally studied. There is in reality no absolute difference between the two subjects; physiological chemistry deals with the question how these substances are made, and what changes they undergo, *in nature*, whereas organic chemistry treats of the changes they *can* be made to undergo by various chemical means in the laboratory, and how they can be synthesised. Synthesis also occurs in nature, but whether it proceeds in a manner similar to

that which Fischer has so subtly carried out has still to be determined. The knowledge of the properties of simple definite chemical compounds has enabled us to separate the amino acids, and thus gain an insight into the ultimate structure of a protein. The study of the polypeptides of definite constitution has led to the isolation of such compounds directly from proteins, and will no doubt help us in finding out the nature of the more complex substances, known as proteoses and peptones. The chemical changes which have given us the most knowledge are the hydrolytic changes, and these are produced by the proteoclastic enzymes, which are more delicate and specific in their action than either acids or alkalies. The study of the action of enzymes upon the proteins and the polypeptides gives us indications as to how the protein may eventually be synthesised, by directing the manner in which we combine together the amino acids to form simple polypeptides, these again into greater complexes, and so on until a protein results. We have seen from the above that this method is being carried out, polypeptides having been not only synthesised, but also isolated directly from the protein, and their identity established.

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SOME RECENT RESEARCH UPON THE BIRTH AND AFFINITIES OF CRYSTALS[1]

By PROFESSOR H. A. MIERS, D.Sc., F.R.S.

The main facts concerning the growth of crystals are familiar to all, and do not require more than the briefest statement. A saturated liquid solution of any substance, A, in any other, B, is a mixture of A and B in the liquid condition, such that if a solid crystal of A be immersed in it the crystals will neither grow nor dissolve. If the solution be ever so slightly weakened by addition of B, the crystal will begin to dissolve till equilibrium is restored; the same effect is in general produced by slightly warming the solution. If, on the contrary, the liquid be ever so slightly supersaturated by removal of B (*e.g.* by evaporation), the crystal will begin to grow till equilibrium is restored; the same effect is in general produced by slightly cooling the solution.

The solubility or freezing-point curve, SS (fig. 1), gives the temperature at which a series of the solutions of different strengths are saturated. It may be experimentally determined by immersing a minute crystal fragment of A in each solution as it cools, and noting the temperature at which the fragment neither grows nor dissolves. If the solution be cooled below the saturation temperature without the insertion of A, and if it be protected from agitation and from exposure to the air, it may often be preserved for a long time in the supersaturated condition without crystallising. Its behaviour is in this respect similar to that of a simple liquid supercooled below its freezing point; the latter can also be preserved for a long time in the supercooled condition without crystallising. The insertion of a fragment of the solid crystalline substance in either at once

[1] This paper embodies the substance of two lectures delivered at the Royal Institution on April 11 and 18, 1907.

causes crystallisation to begin, and the same effect may often be produced by shaking.

> Break thou deep vase of chilling tears
> That grief hath shaken into frost,

are well-known lines from *In Memoriam* that refer to this remarkable effect.

It is curious that no systematic observations have hitherto been made upon the behaviour of solutions which are continuously shaken while cooling.

In the course of some experiments upon the refractive indices of cooling supersaturated solutions of various salts made by Miss Florence Isaac and myself in the Mineralogical Laboratory at Oxford we noticed that when such a solution is stirred in an open vessel, a thin shower of crystals generally appears at or about the saturation temperature; but that after the temperature has fallen about 10° below this point there ensues a dense shower of crystals, which is generally so thick as to make the liquid almost opaque. The sudden weakening of the solution at the lower temperature is accompanied by a sudden fall of the refractive index, which attains its maximum value at this temperature.

On the first day, when we experimented with a solution which we had not previously used, the earlier and thinner showers of crystals did not appear, and the later and denser shower might be somewhat retarded. But in subsequent experiments the thin shower (accompanied by a slight diminution in the rate of increase of the refractive index) occurred at exactly the saturation temperature, and the dense shower (accompanied by an actual diminution of the refractive index) occurred at a perfectly definite lower temperature.

We infer that the first shower takes place because some fine crystalline particles of the dissolved substance get into the solution with the dust of the air, and continue to grow, and that the second shower is due to a different cause.

If this be so, then the same solution enclosed in a sealed glass tube should not yield the first shower.

We have made this experiment with numbers of aqueous solutions of different substances and of different strengths, and have always found that in a sealed tube the first shower is prevented, and that the liquid cannot be made to crystallise

at a higher temperature than that corresponding to the appearance of the second shower in an open vessel. For example, a 48·2 per cent. solution of sodium nitrate is saturated at 26°, and yields the dense shower at 16°; a 51 per cent. solution is saturated at 39°, and yields the dense shower at 30°; and these solutions enclosed in sealed tubes only yield a shower on shaking at 16° and 30° respectively.

During the visit of the British Association to South Africa

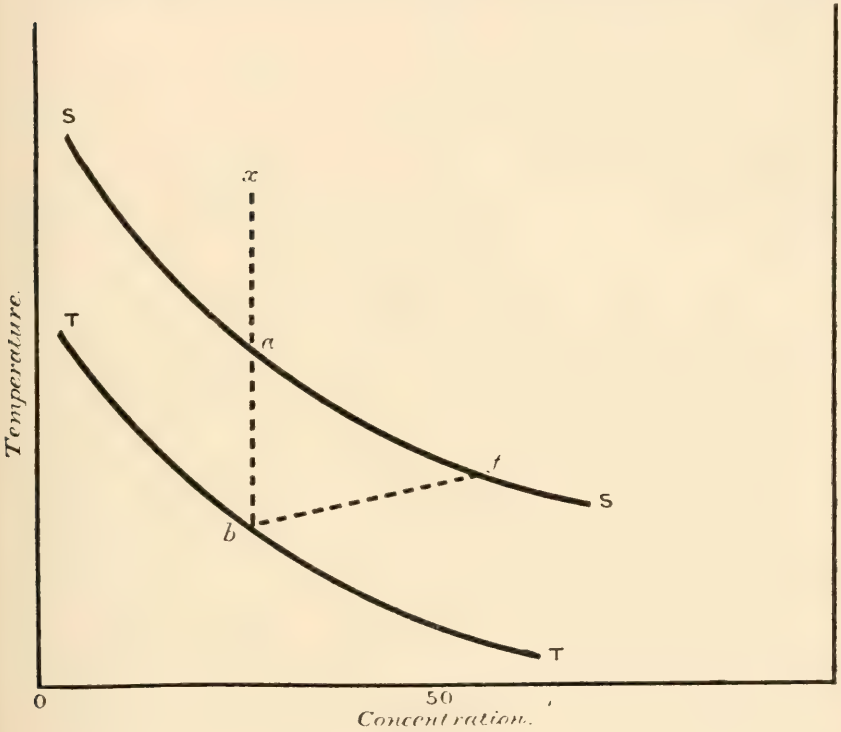

FIG. 1.

I carried sealed tubes containing these and other solutions with me, and during several weeks kept the first solution between the temperatures of 26° and 16°, and shook it violently at intervals without causing crystals to appear. But as soon as the temperature fell to 16° the solution began to crystallise.

We conclude, therefore, that in an open vessel such a solution crystallises at 26° only because the liquid is inoculated by crystal germs from the air, and that it crystallises again at 16° because fresh crystals appear spontaneously or are born in the

liquid. At 26° the cooling liquid passes from the unsaturated condition to a supersaturated one, in which crystals can grow, but require to be introduced from without; at 16° it passes into a condition in which crystals can be made to appear in the liquid by mechanical means such as shaking. Between these temperatures the solution is in what Ostwald has termed the "metastable" condition; below 16° it is in what he terms the "labile" condition: and accordingly we distinguish the two showers, the first by the name "metastable shower" and the second by the name "labile shower."

In any laboratory the air must contain innumerable particles of every material that is being employed in the laboratory, and, so far as we know, immeasurably small germs are sufficient to inoculate a supersaturated solution and make it crystallise; in fact, the crystallisation of an exposed solution must be an extraordinarily sensitive test for the presence of such crystalline germs.

If now the exact temperature at which the dense labile shower makes its appearance be determined for a series of solutions of different strengths, the observations will trace on the temperature-concentration diagram a new line, which we call the "supersolubility curve," giving the relation between temperature of spontaneous crystallisation and strength of solution; this is the curve TT in fig. 1.

We have determined this curve for various solutions such as sodium nitrate and sodium chlorate. We have also, by observations upon the refractive index, traced the changes of concentration in a cooling solution, and we find that it is not possible to obtain a clear representation of what actually occurs without taking account of the supersolubility curve. It is customary to think of a cooling solution as beginning to crystallise so soon as it becomes supersaturated, and as crystallising at such a rate that it remains just supersaturated and no more. If this were so, the changes in the temperature and constitution of the liquid would be represented by the line *xaf*. In reality, unless the cooling be very slow, the order of events is more faithfully represented by the line *xabf*; a few crystals appearing by inoculation at *a* and continuing to grow very slowly, whereas a very rapid growth, which is generally accompanied by a cloud of crystals if the liquid be shaken, sets in at *b*. Messrs. Hartley and Garrod Thomas have traced

the supersolubility curves for triphenylmethane in organic liquids, and have shown how they explain the course of crystallisation even when that substance forms crystalline compounds with the solvent. These authors suggest that the metastable condition is to be explained by the increased solubility which is known to belong to very small crystals. The first products of spontaneous crystallisation must accordingly be more soluble than the larger crystals for which the solubility curve is determined. They cannot therefore persist through the early stages of growth until the degree of supersaturation becomes sufficient to counteract the solubility.

Many peculiarities or apparent anomalies in the crystallisation of solutions can be explained when account is taken of their passage from the metastable to the labile condition.

An experiment familiar to every schoolboy is the scratching of the inside of a test tube containing a strong solution with a glass rod, and the appearance of the first crystals along the line of scratch. This is often explained as due to a tendency of crystals to grow on rough surfaces and protuberances rather than on a flat, smooth surface.

If this explanation were correct, it ought to make no difference whether the scratch be made before or after the tube is filled with the solution, and the crystals ought to appear along the lines of old scratches. In reality, it is necessary that the scratch should be made within the liquid; moreover, we have found that no effect is produced until the solution has been supersaturated to the exact point at which it is becoming labile. The process of scratching merely supplies the mechanical disturbance sufficient to make the crystals grow in the labile solution.

It is true that scratching may produce a line of crystals in a metastable solution; but this only occurs if the rod is introduced from outside, and has caught up crystalline germs in the air or at the surface of the liquid; no effect is produced by scratching with the end of a rod which has been kept in the metastable liquid throughout the cooling.

Now a strong aqueous solution, being merely a mixture of the dissolved substance and of ice, both in the liquid condition, a similar supersolubility curve ought to be obtained for the spontaneous freezing of ice in solutions which contain excess of water. We have not conducted any experiments at sufficiently

low temperatures to trace this curve. But we may confidently predict that for an aqueous solution of a salt which separates in the anhydrous condition—or for a mixture of any two substances which do not form compounds or isomorphous mixtures—the usual V-shaped freezing-point curve of the two components (ME*m* of fig. 2) is accompanied by a V-shaped supersolubility curve (SH*s* of fig. 2) representing their temperatures of spontaneous crystallisation.

[Since writing the above I hear from Mr. Hartley that he and Mr. Barrett have realised the ice supersolubility curve in studying the crystallisation of dilute solutions of sodium sulphite.]

In general, therefore, the cooling of two substances dissolved in each other, whether an ordinary solution, a mixture of two fusible substances, a rock, or an alloy, will be represented by fig. 2, in which M and *m* are the melting points of the two substances A and B, ME and *m*E their freezing-point curves meeting in the eutectic E; S and σ are the temperature of spontaneous crystallisation of A and B when molten and supercooled; SH and σH constitute their supersolubility curve, meeting in what we call the "hypertectic" point H; this is the highest temperature at which they can crystallise spontaneously together.

The process of cooling of a liquid mixture initially of composition X is generally supposed to be represented by the line *xaf*E. The liquid cools down till it becomes saturated at *a* and then cools, with crystallisation of A, always remaining saturated (as represented by *af*E) until at E it reaches the eutectic composition, when B and A can crystallise together without change of temperature, and the whole mass solidifies as the eutectic surrounding the crystals of A.

It will now be clear that this only occurs if the liquid be inoculated with A, be kept stirred, and be cooled extremely slowly. Otherwise supersaturation will occur, and the process is, again, more faithfully represented by the line X*abf*E; crystals may make their appearance by inoculation at the temperature *a*—but at the temperature *b* there will be a sudden access of crystallisation by reason of the spontaneous growth, and some time will elapse before the solution again falls to saturation point at *f*. Or, before this happens, the solution may become labile for B, and that substance may crystallise spontaneously, and so the eutectic mixture may never be attained.

In order to test these predictions we have made experiments

with mixtures of two salicylates, salol and betol, choosing these substances merely because they melt at convenient temperatures, and we have succeeded in tracing for them the complete curves like those shown in fig. 2. By means of the refractive index we have traced the changes in each solution as it cools, and have always obtained curves resembling *abf* of fig. 1. We

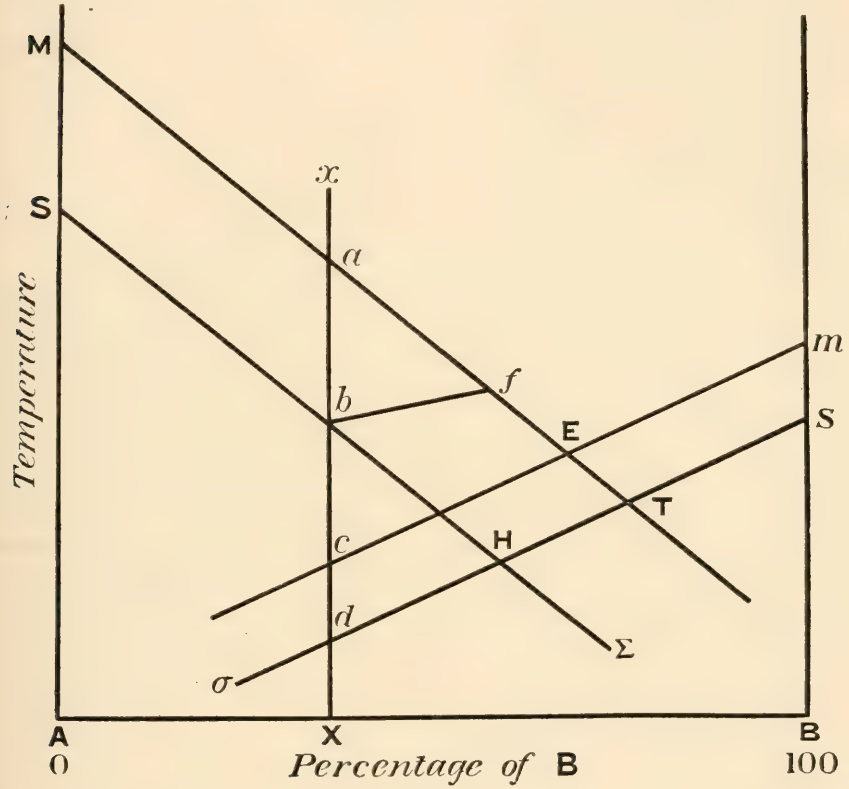

Fig. 2.

have also found that, as is clear from the figure, any mixture has no less than four possible freezing points—namely, two temperatures, *a* and *c*, at which A and B crystallise respectively by inoculation, and two others, *b* and *d*, at which A and B crystallise spontaneously.

The same general principles must hold for mixtures of more than two components; we have already traced the super-solubility curves for mixed solutions of sodium nitrate and lead

nitrate, *i.e.* for mixtures of three components, the two salts and water.

No doubt the same principles prevail in the solidification of metals, alloys, and rocks, although the problem is here complicated by the formation of compounds and isomorphous mixtures (solid solutions); but whatever substance solidifies, it can only crystallise from a solution which is supersaturated with regard to it, and unless this is made to take place by inoculation, the solution must first become sufficiently supersaturated to crystallise spontaneously.

The freezing-point curves terminate at M and *m* in the melting points of the pure substances A and B; and the supersolubility curves terminate at S and *s*, the temperatures of spontaneous crystallisation of A and B. We have determined these for salol and betol. We have also made experiments with water, and have found that pure water contained in sealed tubes crystallises by shaking at $-1{\cdot}9^{\circ}$ C.; and even if heavy substances be enclosed with the water in the tubes so as to produce friction, we have been unable to make it crystallise at a higher temperature than $-0{\cdot}4^{\circ}$ C.

If the crystallisation of a drop of any solution be watched under the microscope, remarkable changes in the process will generally be noticed so soon as the drop passes from the metastable to the labile condition. Experiments made in my laboratory by M. Chevalier have shown that, in a drop of labile solution, potash-alum crystallises as a rectangular network of fine needles, and not in the ordinary octahedra. This observation accords with the general experience that when crystals grow very rapidly they usually grow as needles. I believe this to be due to the fact that when a crystal has started in a labile solution the liquid in immediate contact with it is at once reduced to the metastable condition both by loss of solute and by rise of temperature, so that the growth only takes place within the sheath of less concentrated liquid with which the crystal envelopes and protects itself, and therefore proceeds quite slowly. But if any point of the crystal has begun to advance so rapidly that it projects through this sheath before the zone of weaker solution has time to close round it, then it may continue to advance rapidly through the strongly supersaturated labile solution; and the concentration currents which play most energetically upon the end of a crystal will ensure

that the point is continually in contact with the strong solution, and therefore that the crystal continues to grow rapidly in this direction and slowly in others. That the liquid in contact with a slowly growing crystal is supersaturated but only metastable, I have proved by actually measuring its refractive index. Again, when a rapidly growing needle approaches a crystal at a part of its surface which is growing slowly, it ceases to grow rapidly just before actual contact takes place—*i.e.* so soon as it enters the zone of metastable solution surrounding the latter.

If a thin drop of solution of potassium bichromate be watched as it crystallises on a warm slide, the ring of crystals which form on the edge of the drop will be seen to advance rapidly in a beautiful growth of needles; the process is then suddenly arrested, and the ring continues to grow quite slowly with a thickening of the crystals. After a short interval the sudden growth is repeated, and is then as suddenly checked; and so on until the drop is dry. The explanation is probably the following: the labile solution in which the crystals first appear is reduced in strength by their rapid growth, and falls to the metastable condition, in which the growth is slow—evaporation then raises the strength to the labile point; rapid growth again sets in, and the process is repeated.

Other illustrations of the same recurrent process are to be found (1) in "Liesegang's Rings" of silver chromate produced by a solution of silver nitrate creeping through gelatine which has been impregnated with potassium bichromate; (2) in the stripes of silver chloride deposited in nerve fibres by the operation of acid nitrate of silver acting upon the chlorides in the fibre, as described by Macallum, and in capillary tubes as described by Boehm.

Another feature of crystals growing rapidly in a labile solution is that they are not only apt to grow in long prisms and needles, but to group themselves into the branching and tree-like forms which lend such a beautiful appearance to many of these growths. For example, the frost pattern on a window pane, and the rapid growths of potassium bichromate just described.

This branching of needles is generally due to "twinning," the process by which two crystals grow out of each other in different directions at a fixed angle which depends upon the angles of

their own facets. Twinning can generally be explained as a union of the two crystals along a plane face which is the same in the two crystals, but is reversed in one of them, so that the two crystals grow, as it were, back to back. (Sometimes it is an edge which is reversed.) It is highly probable that twinning is due to the fact that the structures which build up the two crystals can fit together in two positions, either parallel, or the one reversed with regard to the other.

In the rapid and turbulent growth in a labile solution it may well happen that this reversal is more apt to take place than in the more placid growth in a metastable solution. Hence the beautiful stellate groups and tree-like forms which are more characteristic of rapid than of slow growth.

Now just as two crystals of any substance may grow on each other whether in parallel position or in twin (reversed) position, because they have the same structure and fit together in these positions, so it may happen that two crystals of different substances may grow together in parallel position for the same reason. This is well known in such groups as that of the alums, where one alum, if introduced into the solution of another alum, may continue to grow as a single crystal, and become enveloped by the latter—as is clearly visible when the two are of different colours. In such a case the two substances are absolutely similar in chemical composition, only differing by the substitution of metals which exhibit the greatest resemblances in chemical behaviour; and this is no doubt the reason why they possess identical structures. Another still more remarkable case is that of calcite and sodium nitrate. A drop of strong solution of sodium nitrate placed on a clean cleavage surface of calcite at once deposits small rhombohedra which are parallel to one another, and to the rhombohedron on which they are growing. The angles of sodium nitrate are very near to those of calcite, but not identical with them. Further, there is clearly a certain similarity of composition in $CaCO_3$ and $NaNO_3$.

In the course of some systematic experiments upon the parallel growths of different substances, carried out in the Mineralogical Laboratory at Oxford, Mr. T. V. Barker investigated the question whether sodium nitrate also grows in parallel position upon the other minerals of the calcite group, the carbonates of iron, zinc, magnesium, and manganese. He found that

calcite is the only one which possesses this power of bringing down sodium nitrate in parallel position upon itself. Yet calcite is by no means the one which most nearly resembles sodium nitrate in form; in fact, it differs from it in angle more than any of the other carbonates. It is clear then that some other criterion than equality of angle must be applied. On comparing the molecular volumes, however, it is found that calcite is the only one mineral in this group which possesses a molecular volume nearly equal to that of sodium nitrate. A reason why this equality of molecular volume should be essential for a parallel growth to take place is made evident from the following considerations.

In order that two structures of particles may fit together it

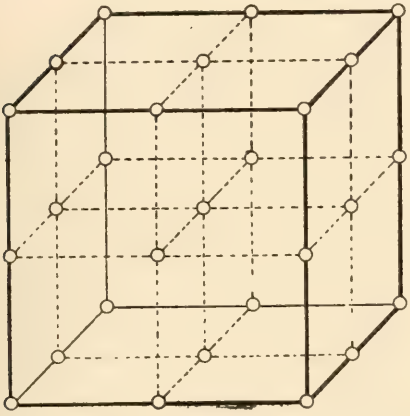

Fig. 3.

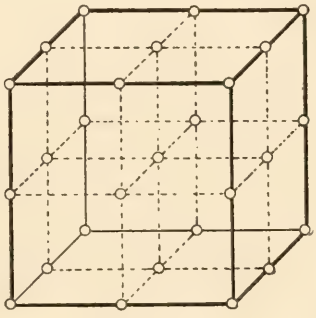

Fig. 4.

is necessary not only that the arrangement of the particles should be the same in both, but also that the spacing of the particles should be identical. Consider, for example, a cubic structure consisting of particles arranged as in fig. 3. The particles are situated at the corners of a series of equal cubic cells. Let fig. 4 be a similar structure, but smaller in dimensions. Both 3 and 4 are cubic structures, and will yield crystals having the same angles; but they will not fit together, because the cubic cells of 3 are larger than those of 4. If the structures are to be identical they must be made up of cells whose volume is the same.

Now the specific gravities, or relative weights of equal volumes, of the two crystals will depend both upon the intrinsic

weight of the particles at the corners of a cubic cell and upon the volume of the cell, and will vary directly as the former and inversely as the latter. The former is, of course, given by the molecular weight—the weight of the atoms of which the molecule consists. If, therefore, the two crystals are to have cells of the same volume, the molecular weight divided by the specific gravity (*i.e.* the molecular volume) must be the same for both. The same principle applies to any two similar structures—not necessarily cubic. The equality of molecular volume accounts, therefore, for the fact that sodium nitrate crystallises in parallel position on calcite alone. That they do possess similar structures is indicated by their similarity of angle, cleavage, and optical and other physical properties.

If this be a true explanation, it must hold good for other groups. Now Mr. Barker has discovered that the alkaline perchlorates and permanganates have the same structure as the mineral sulphates of lead, strontium, and barium (anglesite, celestine, and barytes), as shown by their similarity of angle, cleavage, and constitution.

Among the nine salts examined he found only two, namely, $KClO_4$ and $KMnO_4$, which readily yielded parallel growths on barytes $BaSO_4$ and the other two minerals of the barytes group, and these are precisely the salts which possess nearly the same molecular volumes as the sulphates.

A yet more extensive series has been studied by Mr. Barker, the alkaline haloids which crystallise in the cubic system. No less than seventeen of these were examined, and among the two hundred and seventy-two possible combinations realised, parallel growths were only obtained between those which possess most nearly the same molecular volumes.

[Equality of molecular volume in a series of substances having the same crystalline structure may also be expressed as equality of topic axes, a conception which is rapidly becoming familiar since its introduction by Becke, Muthmann, Tutton, and others, and one which enables us to compare not only volumes, but corresponding magnitudes along parallel directions in such a series.]

In all these groups it seems that when the molecular volumes are almost exactly equal, the parallel growth is so perfect and uniform that it takes place over the whole surface of the crystal, which then appears simply to increase in size by the addition

of the new material. This happens with the alums, as mentioned above.

The researches which I have described in this paper give us, I think, some insight into the invisible structure of the crystal edifice and its manner of growth; they also lead to one other inquiry which has not yet been carried out. Parallel growths take place upon crystals of the same substance; they also take place upon crystals of another substance having the same structure and molecular volume. A crystal of the dissolved substance dropped into a metastable solution at once relieves the supersaturation and continues to grow. Is it the case that the supersaturation can also be relieved by a crystal of some other substance, provided that it has the same structure and molecular volume? I think that this will probably be established by future experiments, for I have found that the supersaturation of a metastable solution of sodium nitrate appears to be relieved by calcite, but not by the other members of the calcite group.

If this be so, the relief of supersaturation and the parallel growth are two occurrences which can hardly be referred merely to the geometrical fitting together of two structures, for this could scarcely force the dissolved substance out of solution. I would rather think of a crystal as an assemblage of vibrating particles, and of the geometrical structure as the expression of some rhythmical motion with which they are endued, so that two crystals which have similar structures are in tune with each other, and respond each to the other's palpitations. Is it not possible that the irregular motions of the liquid substance in solution may respond to the rhythmical motion of the crystal particles of a kindred substance in tune with it introduced into the solution, just as one violin responds to another, and so may be transformed into the regular pulsations which perhaps accompany the building up of a crystalline structure?

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DOUBLE SALTS

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Amongst the substances possessed of the typical properties summarised in the name "salt," chemists have for long known and dealt with a large number of comparatively greater complexity of composition, due to their having been produced from two "simple salts." These "compound salts" are generally well crystallised, and their formation from the simple salts is usually accompanied by elimination or absorption of water of crystallisation (Table II.). As a rule, the two constituent simple salts have a common ion: either the anion, as in the case of two sulphates (*e.g.* K_2SO_4 and $Al_2(SO_4)_3$, $FeSO_4.7H_2O$ and $MgSO_4.7H_2O$), or of two cyanides (*e.g.* KCy and AgCy, KCy and FeCy); or the cation, as in the case of two salts of sodium, or of rubidium, or of potassium (*e.g.* $NaNO_3$ and Na_2SO_4; $Rb_2d-C_4H_4O_6$ and $Rb_2l-C_4H_4O_6$; $HClO_4$ and $KMnO_4$). But instances are known in which all the four ions are different (*e.g.* $Cd_2K_4(C_2O_4)_3Cl_2$). The formulæ

$$mMA + nM'A$$
$$mMA + nMA'$$
$$mMA + nM'A'$$

represent these different types of combination. Of these only the two first, *i.e. compound salts formed from simple salts which have a common ion*, fall within the scope of the subject of this paper, and it may here be noted incidentally that in the predominating number of cases the common ion is the cation. Such combinations divide themselves into three classes, sharply separated from one another (Table I.).

I. The ratio of the quantities of the two constituent simple salts varies continuously, with or without a break in the series, from MA = 0 and M'A = 100 per cent. to MA = 100 and M'A = 0 per cent.

In order to form such compound salts the constituent simple

salts must be isomorphous. The series of combinations thus formed, named *mixed crystals*, are of the nature of *solid solutions*; their physical properties are continuous functions of the composition; their chemical properties are those of the two constituent simple salts, *i.e.* the analytical reactions are those of the ions of the two simple salts. Thus $KClO_4$ and $KMnO_4$ are isomorphous and form mixed crystals of all shades of depth of colour, from almost colourless through pink to deep purple, according to the relative amounts of colourless $KClO^4$

TABLE I

CLASSIFICATION OF COMBINATIONS mMA . nM′A FORMED FROM TWO SIMPLE SALTS MA AND M′A

I. MIXED CRYSTALS	II. DOUBLE SALTS	III. SALTS OF COMPLEX ACIDS
(1) *Composition*		
Series from $m = 100, n = 0$ to $m = 0, n = 100$	m and n = simple whole numbers.	
(2) *The* **physical** *properties of the* **solid** mMA . $nM'A$ *are:*		
additively those of the constituent salts, continuous functions of the chemical composition in terms of the simple salts.	in no definite way related to those of the constituent simple salts.	
(3) *The* **chemical** *properties of* **solutions** *of* mMA . $nM'A$ *are:*		
those of the ions of the simple salts, *i.e.* those of M, M′, and A.		*not* those of the ions of the simple salts MA and M′A, but of ions M and $M'A_{m+n}$.

and deep purple $KMnO_4$ present in the crystals. The same additive relation holds for other physical properties, such as specific volume, refractive index, etc. Moreover, a solution of the mixed crystals will give the reaction for the potassium cation and the perchlorate and permanganate anion. Retgers,[1] through his investigations of the relation between the physical properties and the composition of whole series of such salts, has supplied us with definite principles whereby to recognise *mixed crystals*, the chief interest attaching to this class of complex salts being in connection with the study of isomorphism.

[1] "Zur Kenntnis des Isomorphismus," I.–XII., *Zs. physik. Chem.* 4–20, 1889–1896.

II. The ratio of the quantities of the two component salts is a simple molecular one; in mMA.nM′A m and n are very simple whole numbers. Obviously any series of *mixed crystals* must comprise members the composition of which also exhibits such a simple molecular ratio, and cases of confusion have in consequence not been infrequent; but there is the distinguishing feature that whilst for mixed crystals a variation in the proportion of the simple salts present in the solution from which they are deposited will produce a series of gradually varying composition, in the class now under consideration the number of combinations obtained is very small, generally only one; and when it is more than one, the change in composition is sudden, m and n remaining simple whole numbers. Moreover, in this second class the physical properties, such as colour, specific volume, crystalline form, solubility, etc., etc., are not in any definite way related to those of the constituent simple salts, but generally differ widely from these Thus, to take as an example the easily apprehended property of colour, the following constitute striking cases: white acetate of calcium and green acetate of copper, if brought together in equi-molecular quantities, yield a magnificently deep blue salt of the formula $CaCuAc_4.8H_2O$; colourless LiCl and green $CuCl_2.2H_2O$ give a compound of the formula $CuLiCl_3.2H_2O$, which, in a spirit of unusual rebellion against the predominant blue and green of cupric salts, crystallises in garnet-red needles; and similar examples might be multiplied. Compound salts of this type, when in solution, give the analytical tests of the ions of the constituent salts, and they are termed *double salts*, a name which until comparatively lately was indiscriminately applied also to that kind of complex substances formed from two simple salts which constitutes the third and last class.

III. In this class, as in the preceding one, the ratio of the quantities of the two component salts is a simple molecular one; but the compound salt is distinct from a mixture of the components not merely in respect of the physical properties of the *solid*, but also in respect of the chemical properties of the *solution*. Typical examples of such cases are

$$4KCy + FeCy_2 = K_4FeCy_6$$
$$2KCl + PtCl_4 = K_2PtCl_6$$
$$3K_2C_2O_4 + Cr_2(C_2O_4)_3 = 2K_3Cr(C_2O_4)_3,$$

and it is not necessary to repeat here the evidence for the assertion that in all these compound salts the analytical reactions are not those of the simple salts from which they are formed, or—in modern terminology—that in solution these compound salts have ions different from those of the simple salts from which they are formed. Ostwald, to whom we owe the clear recognition of the characteristics of this type of compound salts and their separation from double salts proper, says: "The name of double salts may not be given to any combination of two salts which gives reactions different from those of the constituents."[1] This was written in 1889. The separation insisted upon is definite and legitimate, and the consequent definition of *double salt* and *salt of complex acid* respectively is easy; yet the principle has been slow in getting fully recognised in standard text-books. In the last (that is, the 1897) edition of the volume of Roscoe and Schorlemmer dealing with metals, we find a definition of double salt which it would be difficult to beat for vagueness.

"The term double salt is applied somewhat loosely to salts formed by the combination of one molecule of one salt with one or more molecules of another salt or of an acid, etc. Thus the substances represented by the formulæ $KF + HF$, $AL_2(SO_4)_3 + K_2SO_4 + 24H_2O$, etc., are called double salts. Very little is known about the constitution of such substances, since they are generally decomposed, at all events to some extent, when they are dissolved in water, although they separate out again unchanged when the solution is concentrated. In many cases they are undoubtedly salts of complex acids or bases."

Does not the suspicion obtrude itself that the vagueness is intentional? Vagueness of any kind cannot be brought as a charge against another writer, who does not follow the rule laid down by Ostwald. Mendeleeff, in a piece of vigorous writing, absolutely repudiates the conception of complex acid radicles, considering it unnecessary. The following is a quotation from the 1905 (the third) English edition of his *Principles of Chemistry*, taken from the paragraph dealing with K_4FeCy_6 and K_3FeCy_6.

"Of these two remarkable and very stable salts, it must be observed that with ordinary reagents neither of them gives the same double decompositions as the other ferrous and ferric salts, nor exhibits the characteristic properties of the potassium

[1] "Dissociationstheorie der Elektrolyte," *Zs. physik. Chem.* 3, 1889, p. 598.

cyanide which they contain." Then, after enumeration of the well-known differences, he continues: "This led the earlier investigators to recognise special independent groupings in them. . . . Such a representation is, however, completely superfluous for the explanation of the peculiarities in the reactions of such compounds as double salts. . . . Every double salt ought to be regarded as a peculiar kind of saline compound; potassium cyanide is, as it were, a basic, and ferrous cyanide an acid element. They may be unstable in the separate state, but form a stable double compound when combined together; the act of combination disengages the energy of the elements, and they, so to speak, saturate each other."

Probably most readers would fail to discover in the above a precise meaning or any meaning at all, and the eminent author must himself have had some misgivings on the subject, as he proceeds to say:

"Naturally, all this is not a definite explanation; but then the admission of a special complex radicle can even less be regarded as such."

With the second part of this statement it is not possible to agree, and I have quoted this view concerning the denotation to be given to the term "double salt" only on account of the prestige of its author, and not because it is one which, as far as I know, has found other supporters. We may therefore consider the term "double salt" to be applied only to such crystalline solids, obtained by the combination in a simple molecular ratio of two salts with generally a common ion, as have physical properties different from those of a mixture of the constituents of the same composition, whilst the chemical properties of a solution of the double salt differ in no way from the sum of those of the constituent salts.

In the memoir of Ostwald already referred to, in which "double salts" were for the first time clearly differentiated from the "salts of complex acids," it was further stated as a characteristic of double salts that their existence is limited to the solid state, and that in solution not only their chemical but also their physical properties are additively those of the constituent salts. This, though true as a limiting case for double salts of slight solubility which are practically completely dissociated in solution, has not been found to hold generally; and it has been possible to supply extensive and varied experi-

mental proof for the existence in solution of double salts, an existence which moreover one would be led to expect theoretically. The methods used in these proofs of course all depend on the comparative measurement of physical properties, the values found for the solution of the double salt XY being compared with those calculated for a mixture of the constituent simple salts from the experimental values obtained for X and Y separately.

The following are examples of such comparative measurements:

(i) *Electrical Conductivity.*—Measurements have been carried out by many investigators, who found that in moderately strong solutions, N and N/2, the double salts are but little dissociated. Thus the differences between the conductivities of $2KCl \cdot ZnCl_2$ and of $2KCl + ZnCl_2$ (calculated) amount to nearly 36 per cent., which greatly exceeds the value of the difference which would be due to the influence on one another of salts containing a common ion.[1]

(ii) *Lowering of the Freezing-point.*[1]—For $2KCy + HgCy_2$ the calculated molecular lowering is by 4·77° greater than that observed for $K_2Hg(Cy)_4$, corresponding to a disappearance of about two and a half molecules (or ions) in the formation of one molecule of the double salt.

Calculated from $2KCy + HgCy_2$.	7·57 + 1·93 = 9·50
Found for K_2HgCy_4	= 4·77
Difference . .	4·73

(iii) *Rotation of the Plane of Polarisation.*—Measurements have shown that, whilst for solutions containing mixtures of salts known not to yield double salts the effect measured is additive, solutions containing substances such as 2KI and HgI_2 show marked deviation from the additive values.[2]

(iv) *Colour.*—The yellow chloride of iron and the colourless chloride of potassium form at 22° C. and above a double salt of the composition $FeCl_3 \cdot 2KCl \cdot H_2O$, which in the solid state is red. A concentrated solution of the mixture of the two simple

[1] Jones, H. C. (and others), "Contributions to our knowledge of the Aqueous Solutions of Double Salts," *Amer. Chem. J.* 22, 1899, p. 5; 25, 1901, p. 349.

[2] Schönrock, "Elektromagnetische Drehung der Polarisationsebene in Flüssigkeiten und Salzlösungen," *Zs. physik. Chem.* 11, 1893, p. 776.

chlorides is yellow at ordinary temperature, showing the characteristic colour of $FeCl_3$; on raising the temperature to about 25°, the colour changes to red, indicating the presence in the solution of the double salt.[1]

These various investigations, taken in conjunction, justify the inference that the existence of double salts in solutions of definite concentration has been established.

All said so far has been solely classificatory and has only brought us to the recognition of the distinctive properties of double salts. Quite separate from this is that side of the study of double salts which since 1887 has stimulated so much interest and has produced so great an output of work. Any historical review of the recent growth of physical chemistry, of the extension of its scope and the deepening of its foundations would doubtless have to say something about the 1887 volume of the *Zeitschrift für physikalische Chemie*; and that not only, or not even chiefly, because this was the first volume of the journal which, initially a sign of the rapidly increasing activity in a special branch of chemistry, has become so instrumental in stimulating that activity, but because in it are contained papers which have already become classical as the starting-point and the foundation for new and most important theories.

In that volume Van't Hoff wrote on "The Part Played by Osmotic Pressure in the Analogy between Solutions and Gases," Arrhenius on "The Dissociation of Substances Dissolved in Water"; and in it appeared another contribution by Van't Hoff entitled "The Transformation Temperature in Chemical Decomposition." This last-named paper was the first in a long series of experimental and theoretical investigations, the results of which are summarised in the book published by Van't Hoff in 1897 under the title *The Formation and the Splitting of Double Salts.* Starting from the observation that the formation of a double salt from its components and the reverse change occur at a definite temperature, above which temperature only the double salt and below which only the two constituent simple salts can exist, or *vice versa*, Van't Hoff, in the pioneer paper referred to, gives those examples which now are found in every text-book of physical chemistry (Table II.). When the simple crystalline

[1] Hinrichsen and Sachsel, "Über die Bildungs- und Löslichkeitsverhältnisse der Doppelchloride des Eisens und der Alkalimetalle," *Zs. physik. Chem.* 50, 1905, p. 90.

sulphates of sodium and magnesium are rubbed together and heated to above 22° the mass liquefies as the result of the formation, accompanied by splitting off of water, of the double sulphate *astrakanite*. Conversely, finely powdered astrakanite, when rubbed with a small amount of water at a temperature below 22°, soon solidifies to a hard mass, which is a mixture of

TABLE II

EXAMPLES OF DOUBLE SALT FORMATION AND DECOMPOSITION

	Transition Point and Transition Interval.	Heat effect in formation of D.S.	Change of hydration in formation of D.S.
I. Astrakanite			
$+\begin{matrix}Na_2SO_4 . 10H_2O\\MgSO_4 . 7H_2O\end{matrix}\rightleftharpoons Na_2Mg(SO_4)_2 . 4H_2O + 13H_2O$	D.S. *formed* at 21·5° and partially decomposed by water between 21·5° and 25°.	Heat absorbed.	Water split off.
II. Cupric Dipotassium Chloride			
$\begin{matrix}CuKCl_3\\+KCl\\+2H_2O\end{matrix}\rightleftharpoons K_2CuCl_4 . 2H_2O$	D.S. *decomposed* at 92°.	Heat evolved.	Water absorbed.
III. Copper Calcium Acetate			
$\begin{matrix}CuAc_2 . H_2O\\+CaAc_2 . H_2O\\+6H_2O\end{matrix}\rightleftharpoons CuCaAc_4 . 8H_2O$	D.S. *decomposed* at 75°.	Heat evolved.	Water absorbed.
IV. Seignette (or Rochelle) Salt			
$\begin{matrix}2Na_2Ta . 2H_2O\\+2K_2Ta . \frac{1}{2}H_2O\\+11H_2O\end{matrix}\rightleftharpoons 4NaKTa . 4H_2O$	Double tartrate *decomposed* at 55° and partially decomposed by water between 41° and 55°.	Heat evolved.	Water absorbed.
V. Scacchi's Salt			
$d.NaNH_4 . Ta . 4H_2O + l.NaNH_4 . Ta . 4H_2O \rightleftharpoons (Na . NH_4 . Ta)_2 . 2H_2O + 6H_2O$	Racemate (double) *formed* at 27° from two tartrates (double), not decomposed by water.	Heat absorbed.	Water split off.

the two constituent sulphates, a change which does not occur if the salt and the water are kept above 22°. He also quotes the case of the green acetate of copper and the white acetate of calcium, which, when powdered finely and moistened with water in the ratio of the equation $CuAc_2 . H_2O + CaAc_2 . H_2O + 6H_2O$, solidify at ordinary temperature to a hard blue mass of the double salt; the latter, when heated to above 78°, again decomposes into the two constituent salts, a transformation which makes itself evident

by the change of colour from blue to green. Van't Hoff recognises these and similar transformations to be of essentially the same kind as those occurring in fusion, of which the reversible change ice-water is the simplest example; or as those occurring in allotropic transformation, of which the reversible change of rhombic to monoclinic sulphur at 96° is an instance. What all these cases have in common is, that the systems concerned are in their composition heterogeneous, *i.e.* made up of non-miscible portions which, themselves homogeneous, are marked off from one another by bounding surfaces, and which can be mechanically separated from one another, such portions having by Willard Gibbs been named *phases*. Moreover, in the changes occurring there is the complete transformation at a definite temperature, named the *transition point*, of one phase into another, and the equilibrium condition is independent of the total amount present of each phase. Thus the formation and the splitting up of double salts—that is, the reversible change of one solid phase into two other solid phases—belongs to the class of *complete heterogeneous equilibria*; and the investigation of the effect on the equilibrium condition of changes of temperature, pressure, and concentration are problems which it has become possible to solve by the application of the phase rule. In the formation of a double crystalline salt which separates from an aqueous solution of the two component simple salts, we deal with a case of three components (viz. the two simple salts and water) which can form five phases: three solid (the two simple salts and the double salt), one liquid (the solution), and one gaseous (the aqueous vapour). But in the formation and decomposition of double salts in contact with solution, which ordinarily occurs in open vessels, there is absence of the possible gaseous phase; moreover, the change of solid phases into one another being accompanied with generally very little volume change, the influence of pressure on the equilibrium condition is practically negligible. These are the two properties characteristic of the special class of heterogeneous systems named by Van't Hoff *condensed systems*. Van't Hoff says: "In the investigation of the splitting up and of the formation of double salts, we follow out a special case of the study of so-called *condensed systems*, which exhibit peculiar transformation phenomena analogous to those of solidification and of fusion. The temperature named the *transition point*

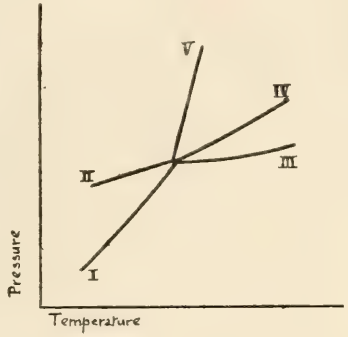
corresponds to the *melting point.* At the outset of his dealings with double salts, Van't Hoff had drawn attention to the fact that co-existence of the three phases double salt, one simple component, and solution, can occur only within a certain range of temperature, and that there is only one temperature (the transition point) at which there can be equilibrium between the solution and the three solid phases double salt and two simple salts.

Soon after, Roozeboom,[1] applying the principle and the terminology of the phase rule, recognised the transition point

TABLE III

THE QUINTUPLE POINT

in the non-variant system composed of three components (*e.g.* Na_2SO_4; $MgSO_4$; H_2O) present in five phases:



(1), (2), (3) Solid { Simple Salt MA . $p H_2O$, *e.g.* $Na_2SO_4 . 10H_2O$
Simple Salt M'A . $p' H_2O$, *e.g.* $MgSO_4 . 7H_2O$
Double Salt $M_m M'_n A_{m+n} . q H_2O$, *e.g.* $NaMg(SO_4)_2 . 4H_2O$

(4) Liquid: Saturated Solution of MA and M'A, *e.g.* Na_2SO_4 and $MgSO_4$

(5) Gaseous: Water Vapour

I. to V. are Vapour-pressure Curves for the Five Univariant Four-phase Systems.

I. for (1), (2), (3) and (5)
II. ,, (1), (2), (4) ,, (5)
III. ,, (2), (3), (4) ,, (5)
IV. ,, (1), (3), (4) ,, (5)
V. ,, (1), (2), (3) ,, (4)

of a double salt as the quintuple point of a non-variant system composed of three components present in five phases, this point being the intersection of curves for five *univariant systems*, each composed of four phases (Table III.).

Roozeboom's paper was followed in quick succession by the publication of much experimental and theoretical work on the lines by him initiated.[2] The greatest amount of attention was

[1] "Die Umwandlungstemperatur bei wasserhaltigen Doppelsalzen und ihre Löslichkeit," *Zs. physik. Chem.* 2, 1888, p. 513.

[2] Meyerhoffer, "Die gesättigten Lösungen der Verbindungen von Cuprichlorid mit Kaliumchlorid," *Zs. physik. Chem.* 5, 1890, p. 96; "Zur Kenntnis der Umwandlungsintervalle," *ibid.*, 9, 1892, p. 641. Vriens, "Dampfspannung des Kupferkaliumchlorids und seiner Lösungen," *ibid.*, 7, 1891, p. 194. Schreine-

devoted to the investigation of solubility relations. The temperature-concentration curves (Table IV.) for the three condensed 3-phase systems, viz.: (1) solution + simple salt MA + simple salt M′A, (2) solution + double salt + simple salt MA, (3) solution + double salt + simple salt M′A, are perfectly analogous to the corresponding temperature-pressure curves (Table III.), in that their intersection marks the transition point, *i.e.* the temperature at which the concentration of the different solutions is the same and at which the three solid phases, double salt and its two constituent simple salts, can co-exist. The graphic representation of these solubility relations has to take account of three variables, (i) the temperature and (ii and iii) the amount present in the saturated solution of each of the components MA and M′A. The most satisfactory manner of doing this is by means of space models with three rectangular axes,[1] though much may be accomplished by means of figures in a plane, such as those reproduced in Table IV. In the projection there adopted[2] the temperature axis is placed vertically, and the values found at different temperatures for the concentration of the two components MA and M′A (expressed as the number of molecules present in one hundred molecules of water) are represented by ordinates on both sides of the temperature axis. Hence two corresponding points such as G and G′, M and M′, etc., always belong together and refer to the same solution, whose concentration with respect to MA and M′A they represent for a special temperature.

The determination over a certain temperature range of such solubility curves, together with an extensive use of graphic methods for their representation, have made it possible to get complete knowledge of the equilibrium condition of the system

makers, "Gleichgewicht des Doppelsalzes von Jodblei und Jodkalium mit wässriger Lösung," *ibid.* 9, 1892, p. 57; and 10, 1892, p. 467; "Graphische Ableitungen aus den Lösungsisothermen eines Doppelsalzes und seiner Komponenten und mögliche Formen der Umwandlungscurve," *ibid.*, 11, 1893, pp. 55–110; "Theoretische und experimentelle Untersuchung über kryohydratische Temperaturen bei Systemen von zwei Salzen mit oder ohne Doppelsalzbildung," *ibid.*, 12, 1893, p. 73.

[1] Of such representations in space, that best known is the carnallite model, Van't Hoff and Meyerhoffer, *Zs. physik. Chem.* 30, 1899, pp. 86 *et seq.* See also Finlay, *The Phase Rule*, pp. 275 *et seq.*

[2] Koppel, "Die Bildungs- und Löslichkeitsverhältnisse analoger Doppelsalze," *Zs. physik. Chem.* 52, 1905, p. 385.

as dependent on the temperature and the concentration of the liquid phase, and also of the effect on the equilibrium condition of changes in temperature and concentration, the latter process being that termed *isothermal evaporation*. Thus the theoretical foundation was within a comparatively short time made so extensive and so firm, that in 1893 the relatively complex relations exhibited by the double potassium-magnesium sulphate could be elucidated with completeness and comparative ease.[1] It is impossible to give even in this paper a short exposition in due order and correct proportion of the theory of double-salt formation, as based on the phase rule. Hence, although recognising the unsatisfactory nature of the undertaking, all it is proposed to do is to say something about such special points or such special aspects as seem to present the greatest interest.

1. *The Experimental Determination of the Transition Point.*— The importance, theoretical and practical, attaching to knowledge of the exact temperature at which the double salt is formed or split, is such as to have led to the working out of a considerable number of experimental methods which it is possible to summarise and to classify into direct and indirect, as shown in Table V. The results obtained by the various methods exhibit not inconsiderable divergence (see values for astrakanite), and the suitability of the application of each of these varies with the special case under investigation. Short of saying a good deal about the technique of the different methods, it is not possible to give an adequate account of this aspect of the subject, and a brief mention of the principle on which they are based is all that can be attempted.

I. In those methods called *direct*, the transition point is found by actually ascertaining the temperature at which occur any of the changes—of volume, energy, appearance—which accompany the formation or the splitting of the double salt. Just as the change at 0° of the *solid* ice to the *liquid* water is accompanied by contraction in volume and absorption of heat, so the transformation of a double salt into the constituent simple salts is accompanied by contraction or expansion in volume (dilatometric method), absorption or evolution of heat (thermometric method), and sometimes also [method I. (iii)] by a change in colour, as in

[1] Van der Heide, "Doppelsalze von Kalium- und Magnesiumsulfat: Schönit und Kaliumastrakanit," *Zs. physik. Chem.* 12, 1893, p. 416.

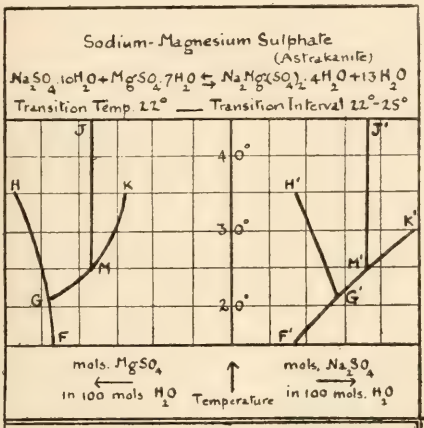
TABLE IV

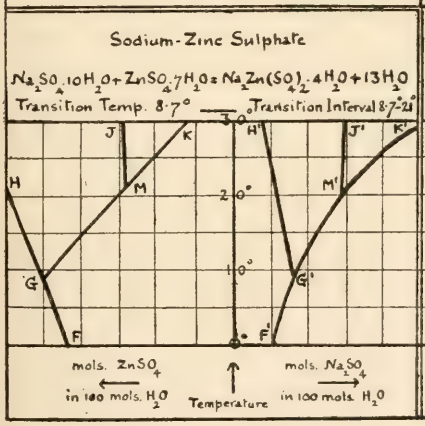
Solubility Curves for Double Salts and the Constituent Simple Salts

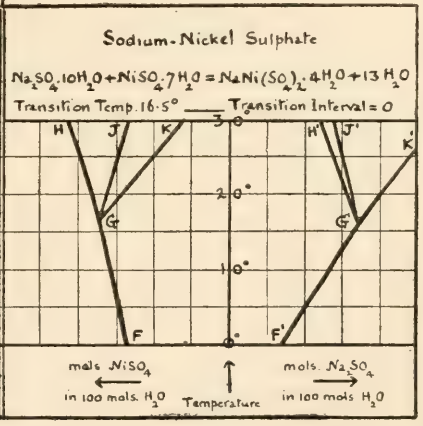
These temperature-concentration curves represent on horizontal axes at both sides of the vertical temperature axis the composition of solutions saturated with two sulphates and in equilibrium with two solid phases.

Curve:	Solid Phases:
FG and FG′	A mixture of the two *Simple Salts* $Na_2SO_4 . 10H_2O$ + $M''SO_4 . 7H_2O$
GK and G′K′	A mixture of the *Double Salt* and *Glauber's Salt* $Na_2M''(SO_4)_2 . 4H_2O$ + $Na_2SO_4 . 10H_2O$
GH and G′H′	A mixture of the *Double Salt* and the *Vitriol* $Na_2M''(SO_4)_2 . 4H_2O$ + $M''SO_4 . 7H_2O$
MJ and M′J′	*The pure Double Salt.*

GG′ is the Transition Point.
MM′ is the end point of the Transition Interval.







the case of the double acetate of copper and calcium (p. 137), or by a change in state of aggregation, as in the case of astrakanite (p. 142).

II. The methods named *indirect* are all based on the principle that at the transition point—that is, at the temperature which marks equilibrium between various states, when

$$m\mathrm{MA} + n\mathrm{M'A} \pm p\mathrm{H_2O} \rightleftarrows \mathrm{M}_m\mathrm{M'}_n\mathrm{A}_{m+n} \pm p\mathrm{H_2O}$$

all the physical conditions for the two systems must be the

TABLE V

EXPERIMENTAL DETERMINATION OF THE TRANSITION POINT IN THE FORMATION AND SPLITTING UP OF **DOUBLE SALTS**

	Results *for Astrakanite*
I. Direct Methods	$\left\{\begin{matrix}\mathrm{Na_2SO_4 \cdot 10H_2O} \\ +\mathrm{MgSO_4 \cdot 7H_2O}\end{matrix}\right.$
Based on finding the temperature at which occur the physical changes (in volume, heat of formation, colour, state of aggregation) accompanying the transformation of one system into the other.	$\downarrow\uparrow$
	$\left\{\begin{matrix}\mathrm{Na_2Mg(SO_4)_2 \cdot 4H_2O} \\ +13\mathrm{H_2O}\end{matrix}\right\}$
$m\mathrm{MA}+n\mathrm{M'A}\pm p\mathrm{H_2O} \rightleftarrows \mathrm{M}_m\mathrm{M'}_n\mathrm{A}_{m+n}\mp p\mathrm{H_2O}$	
(i) Dilatometric	20·6 to 21·6
(ii) Thermometric	22·5 to 22·6
(iii) Observation of change in colour or state of aggregation	between 20 and 25
II. Indirect Methods	
Based on finding the temperature at which the equilibrium conditions are the same for the systems: Double Salt + Single Salt MA + Saturated Solution, Double Salt + Single Salt M'A + Saturated Solution, Single Salt MA + Single Salt M'A + Saturated Solution, *i.e.* when all three or any two of these saturated solutions have identical properties (*e.g.* composition, vapour pressure, etc.):	
(i) Solubility	22
(ii) Tensimetric	20·4
(iii) Electrical	20·7 to 20·9
(iv) Optical.	

same; such conditions are the composition, the vapour pressure, the electrical conductivity and electromotive force, and the refractive index of the *saturated solutions* of the following three combinations of two solid phases: (i) the two single salts, (ii) the double salt and the single salt MA, (iii) the double salt and the single salt M'A. Curves are constructed which represent for *two* or for all *three* of these combinations the variation of these properties with variation in temperature (Tables III.

and IV.), and the point of intersection of these curves gives the temperature sought.

2. *The Action of Water on the Pure Double Salt.*—Experience has shown that whilst some double salts, such as the alums, can at ordinary temperatures be recrystallised from water without decomposition, other salts cannot be so dissolved, and will only crystallise from a solution containing excess of one of the constituent simple salts. This decomposing action of water can be shown in a simple and striking manner in the case of the double lithium-copper chloride already referred to in this paper (p. 137). Even exposure to the moisture of ordinary air quite rapidly effects a colour change from the red of the double salt to the green of the constituent $CuCl_2 . 2H_2O$, a change which occurs instantaneously on moistening the garnet-red crystals with a drop of water; if however, instead of water, a drop of saturated solution of LiCl is used, the colour remains unaltered, showing the non-occurrence of decomposition due to the stability of the double salt in contact with a solution saturated with the more soluble of its constituents.

Other salts again, which like astrakanite dissolve at the transition point (25°) with decomposition and precipitation of the less soluble Na_2SO_4, dissolve at higher temperatures without decomposition. Examination of the curves of solubility (Table IV.) accounts for the above fact, that a pure double salt will at the transition point generally not dissolve without decomposition, and also for the few exceptions to this rule. The two simple salts generally differ in solubility, in consequence of which at the transition point the composition of the liquid phase in equilibrium with the three solid phases is not that of the double salt. Hence, if the double salt in excess is brought into contact with pure water, a greater amount of the more soluble simple salt will go into solution, and there will remain as solid phases the double salt and the less soluble simple salt. Thus, in the case of astrakanite, the component $MgSO_4$ is more soluble than the component Na_2SO_4; and hence, in bringing astrakanite into contact with water less in amount than that required for complete solution, more $MgSO_4$ will be dissolved, solid KCl remaining together with the excess of the double salt. From this it follows conversely that in order to obtain a double salt by crystallisation from a solution of the two components, it is necessary to have the more soluble of these present to the

greater amount required for the saturation of the solution, *e.g.* the copper-lithium chloride is obtained from a solution containing LiCl in considerable excess. But the relative solubilities of the systems involved vary with the temperature, and within the range of the possible existence of the double salt may be found a temperature at which the solution in contact with the double salt and the less soluble simple salt contains the two simple salts in the ratio in which they are present in the double salt; solution of the latter will then take place without decomposition.

The range of temperature between that at which the double salt can begin to be formed, and that at which it ceases to be decomposed by water, is called the *transition interval.* Thus, again taking the case of astrakanite, this salt is formed from the two simple salts at 22°. At a temperature just above this, solubility determinations show that the solution in contact with astrakanite and Glauber's salt contains more $MgSO_4$ than Na_2SO_4, but that at about 25° the two salts are present in equi-molecular quantities, and hence that the double salt will dissolve without decomposition. If the double salt is the stable form below the transition point, the transition interval will extend downwards to a lower temperature. The greater the difference in solubility of the two simple salts, the greater in general is the transition interval, though the temperature coefficient of the various solutions also influences the result. Consequently at ordinary pressures the transition interval is not always comprised within an attainable temperature range, and certain double salts, such as cupric-dipotassium chloride, lead-potassium iodide, can never be dissolved without decomposition. On the other hand, if the two salts have the same solubility at the transition point, a special case which is realised by *d* and *l* tartrates (Table II.), which combine to the racemate, or by sodium and nickel sulphates (Table IV.), the transition interval diminishes to zero, and the double salt dissolves without decomposition.

3. *The Connection between the Heat Effect accompanying the Transformation and the Temperature at which the Transformation occurs* (Table II.).—Some double salts, such as astrakanite, sodium-ammonium racemate, are formed as the temperature is raised, whilst for others, such as copper-calcium acetate, copper-dipotassium chloride, the reverse holds; this means that in some cases the form stable at ordinary temperature is the double

salt, whilst in others it is the mixture of simple salts. Again, some double salts, such as astrakanite and the double racemate, above mentioned, are formed with the splitting off of water, whilst for others the opposite is the case. Now the splitting off of water of crystallisation is generally a concomitant of heat absorption, the taking up of such water of heat evolution. And hence, in the case of the examples quoted—and it is the same in all others investigated hitherto—whenever the double salt is formed on raising the temperature, the transformation is accompanied by absorption of heat and splitting off of water, and *vice versa*, relations in perfect agreement with Le Chatelier's theorem. The heat evolution or heat absorption accompanying the formation of the double salt in each case acts in the contrary direction to the temperature change impressed on the system from without.

4. *Isothermal Evaporation.*—Much practical importance attaches to the consideration of this subject, *i.e.* to the effect produced by changing at constant temperature the concentration of a solution which contains two components capable of existing either as two simple salts or as a double salt. Study of the isothermal curves for temperatures without or within the transformation interval, makes it possible to foretell all the possible cases, and to arrive at rules which prove valuable guides in the practical processes of crystallisation.[1] To follow out this part of the study of double-salt formation, even in its general outlines, is beyond the scope of this paper; but one special case calls for mention, because of its great historical interest in another connection. From the point of view of the theory of double salts, this case is an instance of the difference in the results of an isothermal evaporation according as to whether this is carried out below or above the transition point. Pasteur's preparation of *l* rotatory tartaric acid is justly looked upon as the starting-point of the doctrine of stereo-isomerism, and his own highly dramatic account of the circumstances of this discovery constitutes one of the most attractive incidents in the history of science.[2] To Pasteur, crystallisation of a solution of optically inactive sodium-ammonium racemate yielded hemihedral crystals

[1] Van't Hoff, *Die Bildung und Spaltung von Doppelsalzen*, p. 8 *et seq.*; Finlay, *The Phase Rule*, chap. xvi.

[2] Pasteur, *Researches in Molecular Asymmetry*, Alembic Club Reprints No. 14 p. 20.

of two kinds, which when separated by a process of picking gave two sodium-ammonium tartrates, identical in all respects, except that whilst one was dextro-rotatory like the salt of ordinary tartaric acid, the other was lævo-rotatory to exactly the same amount. The failure of subsequent investigators to produce in crystallisation anything but the double racemate led to a thorough investigation of the whole subject,[1] and to the establishment of the fact that above 28° the double racemate crystallises out, whilst crystallisation below 28° yields a mixture of the two tartrates. Hence it has been said that Pasteur owed his discovery to the *happy chance*[2] that he carried out his evaporation below 28°.

5. *The Carnallite Problem.*—This is a case of technical importance. The potassium chloride used as the starting-point in the manufacture of the many potassium compounds of commercial importance (carbonate, hydrate, cyanide, nitrate, etc., etc.) is found native as the mineral *sylvite*, but by far the larger amount of that required is obtained from the mineral *carnallite*, $KCl.MgCl_2.6H_2O$. This salt has its transition point at 168°, when it breaks up into KCl, $MgCl_2.2H_2O$ and $4H_2O$. Owing to the great difference in solubility between the constituent chlorides, the transition interval is so extended that at ordinary pressure there is no temperature at which carnallite can be treated with water without partial decomposition and separation of the less soluble KCl as a solid phase. This is the principle underlying the old empirical process of the separation of the KCl, which is carried out as follows:

Treatment with water until a solution is obtained, which at 25° is saturated with carnallite, results in the separation of about five-sixths of the KCl in the solid form. The solution saturated for the double salt is evaporated, when carnallite crystallises out, and a solution is produced which for 1,000 molecules of H_2O contains 105 of $MgCl_2$ and 2 of KCl, and which therefore, for practical purposes, may be considered a solution of pure magnesium chloride. This solution is disposed

[1] Van't Hoff, *loc. cit.*, p. 82.

[2] Considering the popular meaning of the term "chance," one would wish to protest against its use in a connection such as the above, and to add some such parenthesis as: "chance, which in the matter of great scientific discoveries with unfailing discrimination and unbroken regularity selects for the recipient of its gifts only the truly great."

of as a waste product, whilst the carnallite that had separated from it is again worked up in the same manner as the original mineral.

Van't Hoff, in his Chicago lectures on "Physical Chemistry in the Service of the Sciences," has pointed out that application of the physico-chemical method to the carnallite problem reveals all the possible methods of splitting it up, methods of which the above process is only one amongst several. He proceeded to suggest another in which, instead of effecting the separation of the KCl by use of the solvent water and concentration of the solution obtained, temperature changes are resorted to in order to produce transformation, melting, and solidification. The process advocated (which has been patented by Van't Hoff's late colleague, Meyerhoffer) is as follows:

The carnallite is heated in closed vessels to 168°, the transition point, when three-fourths of the KCl separates out and is removed by filtration, the water split off retaining in solution all the $MgCl_2$ and one-fourth of the KCl. The liquid is then cooled to 115°, when carnallite crystallises out, leaving a liquid which is an almost pure melted hydrate of $MgCl_2$. The solid carnallite is separated by filtration and again worked up, whilst the liquid, which at ordinary temperatures becomes solid, constitutes the waste product.

The essential difference between the two methods—the empirical and that based on the application of physico-chemical methods—is that in the latter the $MgCl_2$ separated from the KCl is obtained, not as a mother liquor, but in the more convenient form of a solid.

The number of illustrative cases of the application of physico-chemical methods to the special problems encountered in the formation and decomposition of double salts could, of course, be greatly increased; but even the slightest respect for proportion makes it necessary to pass on to another and altogether different aspect of this subject.

The *physico-chemical* method, as developed on the basis of the phase rule, considers the existence of double salts in its dependence on temperature, pressure, and concentration, that is, on factors which it is possible to vary arbitrarily; and in this it differs essentially from the *chemical* method, whose object it must be to find an answer to the question: What relations must exist between two salts in order that—apart

from physical conditions—they may be capable of forming a double salt? Obviously we are dealing here with an affinity problem, and wish to ascertain something about properties fundamentally inherent in different special kinds of matter; we try to learn something about those conditions of double-salt formation over which, in entire difference from temperature, pressure, and concentration, we can exert no influence. In the absence of any means for measuring the affinity between two salts, what work has been done in this province has as yet barely gone beyond the classificatory; but even so, some interesting relations and useful applications have been established. It is proposed to give an account of some of these results, and to do so as shortly as possible under a somewhat arbitrary classification, dealing: firstly, with the work done that bears on the investigation of the relation between the elements which are capable of forming double salts, and the relation between those which are devoid of this power; secondly, with the investigations concerning the effect produced by the substitution of allied elements for one another on the power of forming double salts and on the properties of these salts; and thirdly, with the regularities found, or supposed to have been found, in the formulæ of double salts.

1. As the result of a very large number of experiments, it had long been recognised that an essential factor in the formation of double salts is a certain difference in the chemical character of the two metals. The sulphates of metals such as iron, zinc, magnesium, which crystallise with seven molecules of water, and which are termed *vitriols*, do not form double salts with one another, nor do the sulphates of the very similar elements potassium and cæsium; but there is great tendency to the formation of stable double salts between any one of the vitriols and any one alkaline sulphate. Moreover, the vitriols exhibit that characteristic of the existence of isomorphism which consists in the formation of a series of mixed crystals; and the more marked the chemical relationship, the greater is this tendency, as shown by the absence of any break in the series of the mixed crystals of magnesium and zinc. Similarly, the sulphates of potassium and cæsium are isomorphous. Though the general validity of this view concerning the difference in relationship required for the formation of mixed crystals and double salts respectively had been recognised before, it

remained for Retgers[1] to make it absolutely definite, and to show how it could be applied to argue backwards as to the kind and degree of relationship between different elements. He asserted that two simple salts which form a series of mixed crystals cannot form a double salt, and *vice versa*, that mixture and combination are mutually exclusive, and that this is true without reservation, without any exceptions whatever. Potassium and rubidium and ammonium form isomorphous mixtures, but do not form double salts; potassium and sodium are not isomorphous, but they do form double salts, such as for instance Seignette salt, the double potassium-sodium tartrate, or Scacchi's salt, the double sodium-ammonium racemate, which is a double salt in a double way (Table II.). Sulphates and selenates form isomorphous mixtures, but not double salts, whilst $NaNO_3$ combines with Na_2SO_4 to a double salt. Hence, on the basis of the absolute validity of this relationship, the fact that we know of a number of double salts between potassium and silver, but of none between sodium and silver, leads to the inference of a greater relationship between silver and sodium than between silver and potassium, and points to the probability of isomorphism between silver and sodium, which is proved by the existence of a series of mixed nitrates (and chlorates) of these two metals.

2. Moreover it follows, as a direct consequence of the recognition of chemical difference as the essential factor in the formation of double salts, that the *degree* of this difference ought to be of influence on the relative stability of the combinations produced. That this is actually the case is shown by the numerous instances in which it has been found that the most stable of all the alkali double salts are those of cæsium, itself the most electro-positive of all the metals; and in entire agreement with such incidental and unconnected observations is the result of an investigation on the double chlorides of ferric iron and the alkali metals, which well shows the connection between the stability of the double salt and the gradation in the electro-positive character of the alkali metals.[2] Between 0° and 60° NaCl could not be made to combine with $FeCl_3$; KCl yielded one double salt, viz. $FeCl_3 . 2KCl . H_2O$, whilst CsCl gave two

[1] Retgers, "Über chemische Verbindungen isomorpher Körper," *Zs. physik. Chem.* 15, 1894, p. 529.

[2] Hinrichsen and Sachsel, *loc. cit.*

such salts, viz. $FeCl_3 . 2CsCl . H_2O$ and $FeCl_3 . 3CsCl . H_2O$. It should be noted, however, that no numerical relations emerge from this research, though it allows us to trace the effect on the power of double-salt formation of the substitution of allied elements for one another.

In a later and very extensive investigation of the series of double salts formed between sodium sulphate and the class of sulphates called "vitriols," the realm of the quantitative is being approached.[1] The principle of this comparative study recalls that followed by Mr. Tutton in his extensive researches on the influence on crystalline form produced by the substitution in a series of salts of one isomorphous element for another. The special feature of this investigation of the class of double sulphates, $Na_2SO_4 . M''SO_4 . 4H_2O$ (Table IV.), lies in the fact that the determination of the transition point and the transition interval for each double salt made it possible to examine under strictly comparable conditions what is the influence of the properties of each special vitriol on the properties of the double salt into the composition of which it enters. Thus it could be shown that whenever the vitriol crystallises with seven molecules of water, as happens in the majority of cases (Mg, Zn, Fe", Co, Ni), the double salt crystallises with four molecules; whilst copper and cadmium, whose stable hydrated sulphates contain five and one-half molecules of water respectively, give double salts containing only two molecules; and finally manganese, whose heptahydrate even at ordinary temperatures passes into a monohydrate, gives a tetrahydrated double salt, which however passes into the dihydrate below 40°, that is, at a temperature considerably lower than that of the dehydration of the other tetrahydrated double salts of the series. Connections have also been traced between the solubility of the vitriol and the extension of the transition interval, as well as between the electrical potential of the metal in the vitriol and the transition point of the double salt; but without the reproduction of a large number of numerical data these connections cannot be followed out satisfactorily. The results, moreover, are not very striking; and the chief reason for having said even thus much about this research is to show the method followed in a *chemical* study of double-salt formation.

3. The third and last of my arbitrary subdivisions of the

[1] Koppel, *loc. cit.*

chemical study of double salts deals with the generalisations concerning their formulæ. The record of achievement in this province is but meagre. The double halides are the class of double salts which have been most extensively used in this connection, the reason being that the total number known is very large, and that there is considerable diversity in the combining ratios of the constituents, as many as two or three different combinations between the same simple chlorides being known.[1] Remsen, from a tabulation of a large number of the double halides of the alkalies, has generalised to the effect that the number of halogen atoms due to the alkali metal is always less—or, at least, not greater—than that of the halogen atoms in the salt of the polyvalent metal, *e.g.* $CuCl_2 . 2KCl$, $FeCl_3 . 3CsCl$, etc. This generalisation, known as "Remsen's rule," seems, however, to be far from absolutely valid.[2]

Greater interest attaches to the theoretical speculations of Werner,[3] to the attempt made by him to find in the formulæ of double salts support for his view concerning the numerical values of the valency manifestations of the elementary atoms. Double salts have been amongst the chief of the representatives of so-called molecular combinations, a class of substances about which there has been a good deal of theoretical wrangling, and much discussion barren of practical results. Molecular compounds were, so to speak, merely invented, created in imagination in response to a desire for simplification of valency conceptions; and though furnished from time to time with supposed characteristics to serve as label, the attempt to differentiate molecular from atomic combinations cannot be considered to have proved successful. Werner is attempting to quite banish this conception of molecular compounds, of combinations specifically distinct from the atomic; and to do so he tries to remove by some other means the difficulty for the solution of which they had been created. Structural representation of the composition of double salts, of salts of complex radicles, of crystalline hydrates, etc., on the basis of atomistic combination, requires for

[1] Remsen, "Double Halogen Salts," *Amer. Chem. J.* 11, 1889, pp. 291 *et seq.*

[2] Wells, "Generalisations on Double Halogen Salts," *Amer. Chem. J.* 26, 1901, p. 389.

[3] Werner and Miolati, "Beiträge zur Konstitution anorganischer Verbindungen," *Zs. physik. Chem.* 12, 1893, pp. 35 *et seq.*; *Zs. anorg. Chem.* 3, 1893, p. 267 *et seq.*; 9, 1895, p. 382 *et seq.*

certain of the elements involved the manifestation of more combining units, *i.e.* of a higher valency than that deduced from their simpler combinations, which are the more numerous and the more stable. Now what Werner does is to conceive of two kinds of valency manifestations, the *chief* or *primary* valencies (Hauptvalenzen), which are effective in the compounds from whose composition the ordinary valency values are deduced, and the *subsidiary* or *secondary* valencies (Nebenvalenzen), which are different in nature from the first, as they bind entirely different radicles. The number of "subsidiary" valencies, like that of the "chief" valencies, is limited. He assumes that in compounds of a higher order the atom considered to form the nucleus can bind a definite number of other atoms, independent of the nature of these atoms, monovalent chlorine ranking alike with divalent oxygen. This number, which arises from the joint effect of "chief" and "subsidiary" valencies, is called the *co-ordination* number, and is defined as the limiting number which indicates how many atoms, independent of their valencies, are directly linked with one other special atom. The co-ordination number of an elementary atom can be deduced from the composition of its structurally known compounds, that is, from the maximum number of atoms, radicles, or groups linked with the elementary atom. In the majority of cases this number is found to be *six*, though *four* is of not infrequent occurrence. Thus when, in a simple salt, according to its ordinary valency value, the binding capacity of the metallic atom seems exhausted, it may still possess the power of certain atomic linkings whereby it participates in the building up of more complex molecules. Taking $FeCl_3$ as example, Werner points out how this salt, which by itself appears saturated, yet possesses the power of further combination with three apparently equally saturated molecules of KCl. [The argument is not invalidated by the fact that it has now been proved that the double salt is $FeCl_3 . 2KCl . H_2O$, and not, as Werner had supposed, $FeCl_3 . 3KCl$; the place of one molecule of KCl is taken by one of H_2O.] He says: "It is assumed that in the double salt $FeCl_3 . 3KCl$ all the six Cl atoms are linked with the Fe atom, that it contains the radicle $FeCl_6$, whose existence finds its explanation in the capacity of the iron to directly link six atoms—that is, in the co-ordination number six. Hence the co-ordination number is intended to represent that property of the atoms which makes

it possible to refer back the so-called 'molecular compounds' to actual linkings between quite definite atoms." An examination of the formulæ of the double salts dealt with in the course of this paper, will show that the majority of them support Werner's hypothesis; thus, for the double chloride of copper, the double sulphates of the astrakanite type, the co-ordination number is six. But at the same time there are undoubted exceptions, such as $FeCl_3 . 3CsCl . H_2O$, for which the co-ordination number would be seven; $CuCl_2 . LiCl . 2H_2O$, for which it would be five. It remains for future work to show how far these and other exceptions can be accounted for, and how far the hypothesis will prove deductively fruitful. At the present time it certainly marks an interesting attempt at simplification.

THE MECHANISM OF TISSUE RESPIRATION

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It is a fundamental property of all living organisms to be continually giving off carbon dioxide, and for all except certain bacteria and parasites to be continually absorbing oxygen. With these processes of respiration most of the so-called vital properties of protoplasm are so intimately bound up that, could we unravel them in their entirety, we should be not far from solving the mystery of life itself. How very remote we are from even a partial solution of the problem will be evident from the pages of this article, but we have at least made some progress towards it within recent years.

And firstly, how far are the carbon-dioxide-producing powers and oxygen-absorbing powers of living tissues dependent on one another? It would seem at first sight that they are but little related, for it was shown by Spallanzani in 1803, and since then by Johannes Müller and others, that animals such as the frog continue to exhale CO_2 even when entirely deprived of oxygen. In 1875 Pflüger repeated these observations, and he found that frogs, when kept in nitrogen containing no trace of oxygen, continued to give out CO_2 for several hours, at a rate but little inferior to that exhibited by frogs kept in air. Aubert made some direct comparisons of the CO_2 discharge of frogs kept in air or in nitrogen in a large glass cylinder over mercury. The experiments lasted four hours as a rule, and they were made at temperatures varying in different cases from 3·6° to

19·5° C. For purposes of comparison the results obtained have been grouped together and means taken.

Frogs kept in Air.			Frogs kept in Nitrogen.		
Number of Experiments.	Temperature.	CO_2 per hour per Kilogram.	Number of Experiments.	Temperature.	CO_2 per hour per Kilogram.
5	3·6° to 9·6°	24 c.c.	9	3·6° to 9·8°	24 c.c.
4	10·0° „ 14·5°	46 c.c.	3	11·3° „ 13·8°	43 c.c.
2	18·0° „ 18·5°	72 c.c.	8	15·0° „ 19·5°	70 c.c.

From these mean results we see that the CO_2 discharge of the frogs kept in nitrogen was practically as great as that of frogs kept in air, and that it was influenced to the same extent by rise of temperature. The lack of oxygen, though at first producing no obvious effect either in the CO_2 discharge or the vitality of the frogs, did so after a time, and the higher the temperature at which the experiment was carried out the sooner were the effects produced. The movements of the frogs became gradually feebler, and then ceased, though the heart continued to beat long after the nervous system was completely paralysed, and the CO_2 discharge continued to some extent even after cessation of heart-beat. At a temperature slightly above zero the frogs' movements continued as long as seven days. At 7° C. they continued for eight hours on an average, and at 12° for five hours; but at 21° they ceased in seventy-two minutes, and at 27° in twenty-five minutes. Though the CO_2 discharge persisted for longer than these periods, it slackened off very quickly at the higher temperatures, and so it was found that the *total* volume of CO_2 given off by the frogs was practically independent of the temperature. There seems to be a more or less fixed volume of CO_2 in the tissues of the frog, and this volume can either come off very slowly at a low temperature, or rapidly at a high one. Aubert did not attempt to fix the volume exactly, but he found that whether the frog were kept in nitrogen for 1,383 minutes at 7.9°, for 575 minutes at 11·8°, for 110 minutes at 22·8°, or for 35 minutes at 27·5°, it almost always gave off about 200 c.c. of CO_2 (reckoned per kilogram of body weight).

The CO_2 discharge in a nitrogen atmosphere has been measured also in the case of a snail (*Limax agrestis*) and a caterpillar (*Tenebrio molitor*). Thunberg, who carried out these

observations, found that with both these organisms the CO_2 discharge showed an immediate and progressive diminution from the moment the nitrogen was substituted for air. For instance, three snails kept in air at 19·6° gave out CO_2 at the rate of 322 c.c. per kilogram per hour. In nitrogen the rate of discharge dropped in successive half-hours to 202, 136, and 104 c.c., and then for the remaining five hours of the experiment to 80–90 c.c. Altogether 644 c.c. of CO_2 were given out in six and a half hours, whilst in another experiment at the same temperature no less than 1,088 c.c. were given out in the same time. These animals, therefore, contained a very much larger amount of separable CO_2 in their tissues than frogs do, for even at the end of these two experiments the CO_2 was still coming off at a fairly rapid rate. The caterpillars experimented with did not show quite so remarkable a result as this, but in six and a half hours at 17·5° they gave out CO_2 amounting to 446 c.c. per kilogram, and during a further twenty-two hours they gave out 532 c.c. more, or 978 c.c. in all.

In the case of warm-blooded animals it is obvious that exposure to an atmosphere of nitrogen would cause death and cessation of CO_2 discharge in a very few minutes. A liberation of CO_2 by the tissues does not absolutely cease, however, for the writer found that if an excised mammalian kidney be perfused with oxygenless saline it continues to give off CO_2 for some hours. This CO_2 rapidly dwindles down, and after an hour or two falls to 15–14 c.c. per hour per kilogram, but it was found that altogether nearly 100 c.c. per kilogram was discharged. The amount varied but little, whether the temperature of perfusion were 15°, 20°, or 28°, just as Aubert found it to vary but little in the frog. Whether mammalian tissues as a whole contain much less separable CO_2 than amphibian tissues it is impossible to say, for it is probable that the CO_2 stored up in the different organs of an animal varies considerably, being, for instance, large in muscle and small in nerve. But at least we may conclude that it is very much larger in the snail than in the caterpillar, and in the caterpillar than in the frog.

And by what processes is this CO_2 formed in the tissues in the absence of oxygen? Engelmann, Pflüger, and others suppose that the protoplasm of the cells, when exposed to oxygen, has the power of binding it and storing it up in an intramolecular

form, and that this store of combined oxygen confers upon the protoplasm its peculiar properties of instability and excitability. Further, it is supposed that once the store is exhausted, excitability is lost, or, conversely, that the persistence of excitability in living tissues after total deprivation of oxygen implies the existence within them of intramolecular oxygen. This hypothesis of intramolecular oxygen has been generally accepted, for it offers a reasonable explanation not only of the above-recorded facts concerning CO_2 production, but of many others. If the capacity of an organism or tissue for CO_2 production be a measure of its capacity for storing up intramolecular oxygen, then it follows that this capacity varies between very wide limits—*e.g.* as 100 to 1,200 or more. However, we know that at least some of the CO_2, and probably a great deal of it, arises in other ways than by intramolecular oxidation. The blood and lymph of mammals, and presumably also of the frog, contain 40 to 50 per cent. of their volume of loosely bound CO_2. Now we know that two-thirds or more of the total weight of an animal consists of water, only a small part of which is present in the blood and lymphatic vessels. Most of it is found within the cells, and this intracellular fluid, for aught we know to the contrary, may contain as much loosely bound CO_2 as the lymph of the lymphatics. If this were the case, then the total body fluids would contain about 300 c.c. of loosely bound CO_2 per kilogram, and if only two-thirds of it were liberated in frogs kept in an atmosphere of nitrogen, it would be unnecessary to assume that any of it was formed from intramolecular oxygen. Unfortunately no determinations have been made of the acidity or alkalinity of the blood and tissues of the frogs at the end of the experiments, or of the CO_2 set free from them on acidification, as compared with that from the blood and tissues of normal frogs. As we shall see later on, there can be very little doubt that acids are formed in the tissues under the conditions of the experiment, though we cannot say in what amount. The discharge of CO_2 by an organism kept in absence of oxygen is therefore no unequivocal proof of the existence of intramolecular oxygen in the tissues, though the estimations by the writer of the CO_2 discharged from mammalian kidneys on perfusion with oxygenless saline seem valid, and it was proved that in their case perfusion with dilute lactic acid provoked no liberation of CO_2.

Other proofs of the existence of intramolecular oxygen are mostly of the type first brought forward by Engelmann in 1868. Engelmann kept ciliated epithelial cells in an atmosphere of hydrogen till all movement ceased, and then added sufficient oxygen to start the movements again. On replacing this mixed atmosphere with pure hydrogen, it was found that cessation of ciliary movement ensued earlier than on the first occasion. The longer the cells were kept in oxygen, however, the longer time did the ciliary movements persist in the hydrogen, so it looked as if the cells had been able to store up a supply of intramolecular oxygen on which they could gradually draw. Again, Öhrwall found that if the flow of perfusion liquid through an excised frog's heart (kept in a hydrogen atmosphere or in salt solution) were stopped, the heart ceased beating in one to three hours. If the perfusion were resumed, the heart speedily began to beat again; but if the perfusion were now stopped it ceased beating in four to twenty-five minutes—*i.e.* in a very much shorter time than previously.

Experiments of a similar nature have been made by Bernard upon fish, and by Frohlich and by Baglioni upon nerve; but, as Winterstein points out, none of these results afford convincing proof of the existence of intramolecular oxygen. Winterstein, indeed, denies the existence of this oxygen, and he supposes that the loss of excitability produced by deprivation of oxygen is due to the accumulation of toxic products of fatigue. In the presence of free oxygen, these products are gradually oxidised and rendered harmless, and so it follows that if the inexcitable tissue be exposed to oxygen for only a short time, but small amounts of the toxic products are oxidised, and so a second deprivation of oxygen induces a much speedier loss of excitability than the original deprivation did. This explanation might be held to be negatived by an interesting experiment of Verworn's, in which a frog was perfused with oxygen-free salt solution. Strychnine was added to the saline so as to heighten the excitability of the cord, and for some minutes each stimulation of the skin resulted in a succession of brief reflex muscular contractions. If during this initial period the flow of oxygenless saline were stopped, the cord speedily lost its reflex excitability; but if the flow were resumed again, it was found that the excitability might return for a short time. It then disappeared permanently so long as the flow of oxygenless saline was continued,

and could only be brought back again by the substitution of oxygenated saline. Verworn thought that the first brief recovery of excitability was due to the oxygenless saline washing away the products of fatigue from the tissues, and that the tissues still retained a small amount of intramolecular oxygen. Once this was used up, however, no further recovery of excitability was possible until the tissues were supplied with more oxygen from external sources.

Even this experimental proof, ingenious at it is, does not finally prove the point at issue, for it is possible that some of the toxic products of fatigue are soluble, and that the removal of these products by oxygenless saline leads to some recovery of excitability. Other of these products may be insoluble, and only be removable after oxidation by free oxygen.

Still another type of argument in support of the doctrine of intramolecular oxygen is derived from a study of the respiratory quotients yielded by an animal before, during, and after deprivation of oxygen. For instance, Thunberg observed that caterpillars kept in air gave a quotient of ·81. On substituting an atmosphere containing 99·5 per cent. of nitrogen and ·5 per cent. of oxygen, their oxygen intake fell to about a tenth of its previous value, whilst their CO_2 output fell to about a fifth—*i.e.* the respiratory quotient became double the normal. On returning the caterpillars to air again, the CO_2 output increased considerably—though it was never more than half its original value—but the oxygen intake increased in a still greater proportion, and respiratory quotients of ·64, ·67 and ·70 were obtained in successive half-hour intervals. Relative to their CO_2 output, the caterpillars were therefore absorbing oxygen at a greater rate than usual, apparently in order to replenish the stock of intramolecular oxygen they had drawn upon during the nitrogen period. The writer obtained similar results with mammalian kidneys, though he found that the extra volume of oxygen absorbed on substituting oxygenated saline for the previous oxygenless perfusion liquid was only a third to a half as great as would be expected from the output of CO_2 during the oxygenless period.

But this type of result can likewise be explained on the hypothesis of fatigue products. Such products, if insoluble, may collect in the tissues during the oxygenless period, and require

an extra amount of oxygen for their complete removal during the subsequent oxygen period. To take a concrete instance, one suggested by Winterstein, the decomposition of a carbohydrate molecule may take place in the following two stages:

$$C_6H_{12}O_6 = 2C_2H_6O + 2CO_2.$$
$$2C_2H_6O + 6O_2 = 6H_2O + 4CO_2.$$

The change represented by the first equation results in the formation of a third of the total CO_2 output, though no oxygen is drawn upon whatever; whilst according to the second equation the complete oxidation of the alcohol— a "fatigue product" produced by the first decomposition—requires 6 volumes of oxygen for every 4 volumes of CO_2 formed, or yields a respiratory quotient of ·67.

Arguing against the somewhat inconclusive evidence of the existence of intramolecular oxygen, Winterstein adopts the views long since suggested by Detmer, that the primary source of the energy developed in living organisms is not of an oxidative nature, but consists rather in the disintegration of highly complex labile compounds, the decomposition products of which subsequently undergo oxidation. That under certain conditions vital energy *can* be developed in the absence of contemporary oxidation is undoubted, for we know that certain bacteria, as *B. anthracis* and *B. tetani*, live and flourish best under completely anærobic conditions. It seems very probable, also, that some of the energy liberated in ærobic organisms may be of similar origin, but we cannot for a moment imagine that all the energy is developed in exactly the same way. Much, perhaps most of it, is in all probability formed as the result of contemporary oxidation. If this is the case, then a supply of immediately available intramolecular oxygen is essential, and arguing from the weight of evidence, which is admittedly not quite conclusive, we should provisionally adopt the doctrine of its existence.

We must now pass on to a discussion of what is actually known as to the processes of oxidation in the tissues. Mention has frequently been made in the above pages of the collection of fatigue products in the tissues, which subsequently undergo further oxidation; but are such products matters of fact, or mere figments of fancy? Some of the most interesting evidence

bearing upon this question is that obtained by Fletcher in his studies upon the respiration of excised frogs' muscles. A slow current of air or other gas was drawn over the muscle or muscles placed in a suitable chamber, and the CO_2 given off absorbed by baryta and estimated by titration. On tetanising the muscles kept in air or in nitrogen for periods of 10 to 30 minutes, little if any increase in the CO_2 output was observed, provided that the muscles did not, as the result of fatigue, pass into a state of rigor mortis. If this was the case, then the increase of CO_2 might be considerable, and the increase observed by Hermann on tetanisation of muscle is probably to be ascribed to this cause. When, on the other hand, the muscles were kept in a current of pure oxygen, not only was the output of CO_2 during the resting stage increased, but on tetanisation it became more than doubled in amount. For instance, five gastrocnemii in a current of nitrogen gave out ·05 c.c. of CO_2 per half-hour during rest, and ·07 c.c. during tetanisation. Five other gastrocnemii (taken from the opposite limbs of the same five frogs), when kept in oxygen, had at first an output of ·08 c.c. of CO_2 during rest, and ·14 c.c. during activity, and later on an output of ·095 c.c. during rest and ·23 c.c. during activity. It was also noted by Fletcher that fatigue came on much more rapidly in muscles kept in air or nitrogen than in those kept in oxygen, and that fatigued muscles, if allowed to rest in oxygen, recovered much more rapidly and perfectly than if allowed to rest in nitrogen. Still again, he noticed that muscles kept in oxygen never passed into rigor mortis at all. They survived many hours—sometimes as much as fifty hours—longer than muscles kept in nitrogen or air, and then underwent a gradual lengthening instead of shortening. These and other results are most readily explained by supposing that during the resting stage, and still more during activity, there is a continual breaking down of complex molecules in the muscle substance into simpler ones, but that these simpler molecules do not reach their final CO_2 stage except in the presence of free (or intramolecular) oxygen, and that within certain limits the more plentiful the supply of oxygen the more complete and rapid is the oxidation. In an excised gastrocnemius oxygen can only reach the tissue cells by diffusion from the outside, and hence the inner layers of a muscle kept in oxygen would be very much more adequately oxygenated than those of a muscle kept in air.

As to the intermediate products of muscle activity, there is not much definite information, but undoubtedly sarcolactic acid is one of them. The recent results of Fletcher and Hopkins show that absolutely fresh muscle (of the frog) contains only traces of lactic acid (·015 per cent. or possibly less). Fatigued muscle, on the other hand, may contain a considerable amount of lactic acid (·11 to ·21 per cent.), and rigored muscle still more (·24 to ·40 per cent.). The amount of lactic acid any given muscle can develop seems practically constant, whether it be formed suddenly by exposing the muscle to a temperature of 45°, or more slowly by tetanising the muscle when placed in an atmosphere of hydrogen or oxygen, and finally inducing heat rigor. It is formed gradually in resting excised muscle, if this muscle be kept in an atmosphere of hydrogen or nitrogen, *i.e.* under anærobic conditions, but if kept in air it is formed only very slowly, and if kept in oxygen it is not formed at all. On the contrary, as might be expected from Fletcher's results on the restorative power of oxygen on irritability, if muscles in which a considerable lactic acid formation has been induced by tetanistion are placed in oxygen, a good deal of this lactic acid disappears. Such disappearance of lactic acid was found to be dependent on the integrity of the muscle, no diminution showing itself in chopped-up muscle.

Other evidence of lactic acid formation was obtained by Spiro, who found that blood collected from the carotid of a dog in which the muscles of the hind limbs had been tetanised for an hour and a quarter showed quite an appreciable increase of sarcolactic acid. Again, Max von Frey and Gruber found that if an isolated muscle of the dog were perfused with an artificial circulation of blood, and were made to contract, there was a considerable increase in the absorption of oxygen, but a by no means corresponding increase in the output of CO_2. There was a striking rise in the sarcolactic acid in the blood, however, which more than accounted for the deficiency of CO_2. Presumably this acid was not oxidised further in the tissues owing to the abnormal conditions of experiment, but it is possible, as suggested by Von Frey, that even in the intact living animal the lactic acid formed in the muscles may be to some extent oxidised elsewhere. In support of this view may be quoted the observations of Meyer, who found that the diminution of CO_2 production induced by arsenic and phosphorus poisoning was accompanied

by an accumulation of lactic acid, especially in the liver: also those of Araki, who showed that lactic acid appeared in the urine of animals poisoned by carbon monoxide, phosphorus, or arsenic.

The writer has obtained further evidence of the incompleteness of tissue oxidation under abnormal conditions by experiments upon excised mammalian kidneys. When these organs are perfused with oxygenated Ringer's solution for ten or twelve hours, their vitality gradually diminishes, but the processes of tissue oxidation, though gradually becoming feebler in magnitude, do not lack completeness, and the respiratory quotient remains practically constant at about ·85. Kidneys which previous to perfusion have been heated for half an hour to 50° to 60°, or frozen solid and thawed, or been kept in a moist chamber for three to nine days after excision, or poisoned by hydrocyanic acid, likewise show considerable diminution in their gaseous metabolism, but the processes of tissue oxidation still remain complete, and the respiratory quotient keeps at about ·85. When, on the other hand, a kidney was perfused with oxygenated saline solution containing ·06 to ·10 per cent. of lactic acid, or ·005 to ·025 per cent. of free ammonia, its oxygen-absorption power rapidly diminished, but its CO_2-producing power fell off more rapidly still, so that after four to eight hours of perfusion its respiratory quotient dropped to ·46 – 36, *i.e.* to about half the normal.

All the experimental evidence available tends to show, therefore, that the processes of tissue oxidation take place in more than one stage, and that the earlier stages are more readily accomplished than the final stage which leads to the production of free CO_2. How numerous or complex these stages are we have no definite means of knowing, but it is by no means improbable that they are of a comparatively simple nature. It is well known that increased functional activity of muscles or other organs, though it may lead to a tenfold increase of oxygen absorption and CO_2 production, has no effect whatever upon their nitrogenous metabolism. Hence Verworn supposes that only non-nitrogenous groupings or side chains in the "biogen molecules" of the protoplasm are concerned in the ordinary processes of tissue respiration, and he suggests that these side chains may be carbohydrate groupings of an aldehyde character. Also he supposes that intramolecular oxygen is stored up in the

biogens in the form of an NO_2 grouping attached to a benzene ring, and that one atom of oxygen from the NO_2 oxidises the $-CHO$ or $-CHOH$ groups of the carbohydrate molecule to CO_2 and water.

The hypothesis that the respiratory processes of tissues are carried out by non-nitrogenous side chains is borne out by some curious and unexpected results obtained by the writer. It was found that when recently excised mammalian kidneys were perfused with saline solution, the protoplasm of the tissues was in a state of such extreme instability that it was liable to undergo sudden disintegration, whereby a good deal of proteid, proteid decomposition products and intracellular ferments (such as erepsin) passed out into solution. In various experiments carried out under normal conditions, from 9 to 17 per cent. of the total proteids present in the kidney tissues were washed out during the course of an eleven-hour perfusion, and yet the respiratory powers of these kidneys were just as great as those of other kidneys in which there had been little or no tissue disintegration.

The carbohydrate-like nature of the side chains receives support from the above-mentioned facts concerning lactic acid formation in the tissues. We know that sugars are converted into lactic acid not only by the action of various bacteria, but also by intracellular enzymes such as the lactacidase enzyme of the expressed juice of yeast (Buchner and Meisenheimer). Such lactic acid formation may be a normal stage in the oxidation of the carbohydrate-like chains to CO_2, or it may be an exceptional one, occurring but seldom unless the conditions of oxidation in the tissues are deficient. If the $-CHOH$ groupings of the carbohydrate side chains are oxidised one at a time, they would presumably pass through an aldehyde stage first. That an aldehyde stage does occur at some point or other in the course of tissue respiration, seems to be borne out by some observations of the writer. Thus it was found that if an excised mammalian kidney were perfused with saline containing ·1 to ·2 per cent. of hydrocyanic acid, its gaseous metabolism, when estimated shortly after in the usual way by perfusion with normal oxygenated saline, was at a minimum at first, but that it steadily increased for the next eleven hours. During the perfusion, small quantities of HCN broke away from the tissues, and hence it was surmised that this HCN was bound up to $-CHO$ groups so as to form

– CH(CN)OH groups, and that as long as it was so bound the tissues lost their respiratory powers. Similar results were obtained by perfusing kidneys with saline containing ·2 per cent. of acid sodium sulphite. On subsequent perfusion with oxygenated saline the gaseous metabolism of the tissues rapidly increased, and after ten hours became more than double its original value. This result was presumably dependent on the well-known powers possessed by aldehydes of combining with acid sulphites.

Small as is our knowledge concerning the possible or probable course of oxidation of carbohydrate groupings in the biogen molecules, that concerning fats is still less—in fact, it is non-existent. In the fats we have chains of $-CH_2$ groupings, instead of –CHOH groupings, and probably these groupings are oxidised gradually, one by one, as we assumed the –CHOH groupings to be. Proteids may undergo oxidation in more or less the same way, their constituent amino-acid groupings first splitting off ammonia, and then undergoing oxidation in the same way as the fats.

Still one more question remains for our discussion—viz. that concerning the relation of tissue respiration to oxygen tension. We saw that caterpillars kept in an atmosphere of nitrogen containing only ·5 per cent. of oxygen absorbed only a tenth as much oxygen as when they were kept in air, but what would be the extent of oxygen absorption with atmospheres of intermediate composition? To determine this, Thunberg has made a large number of estimations at various oxygen tensions, and some of his mean results are given in the table:

Percentage of Oxygen in Atmosphere.	Mean Oxygen Absorption.	
	Caterpillar (*Tenebrio*).	Snail (*Limax*).
1	46	—
5	83	46
10	93	73
21	100	100
50	—	117
90	—	122

In each series the absorption power in air is taken as 100, and we see that in the case of the caterpillar the oxygen absorbed

increased with the tension, rapidly at first, and then more and more slowly. In all probability the caterpillars kept in air were absorbing oxygen almost at their maximum rate. In the snail, however, the affinity of the tissues for oxygen was so small that from the 5 per cent. mixture only half as much oxygen was absorbed as in the case of the caterpillar, and the maximum absorption rate was not attained in an atmosphere containing 50 per cent. of oxygen. In mammals it would appear that the affinity of the tissues for oxygen is very much greater than in these lowly organisms, for the maximum absorption rate is attained at very much smaller tensions. More than a century ago Seguin and Lavoisier showed that the oxygen absorption was, within certain limits, independent of the oxygen content of the atmosphere breathed. This question has since been repeatedly examined by other observers, and the general consensus of opinion upholds the original doctrine. Löwy, for instance, has found that the oxygen absorption is constant whether the oxygen in the atmosphere breathed be increased to more than double the normal, or diminished to less than half the normal. Of course it does not follow that the tension of oxygen in the blood reaching the tissues varies to the same degree as that in the air respired, but there can be no doubt that it can vary within wide limits without affecting the gaseous metabolism of the tissues. In the case of excised mammalian kidneys, the writer found that at a temperature of 20° the oxygen absorption diminished if the tension of oxygen in the einals used for perfusion fell below half atmospheric pressure, but otherwise it was unaffected.

Pflüger endeavoured to account for this constancy in the oxygen-absorptive capacity of an animal by supposing that through the metabolism of the cells in any given moment only a fixed number of oxygen-binding affinities are liberated, and hence that any further increase in the available oxygen above that required by them is without influence. On this view the tissues must have more oxygen at their command than they can use up, or be always saturated to their full capacity with intramolecular oxygen. Thunberg explains his results by supposing that the restitution of the intramolecular oxygen absorbed in the metabolism is a somewhat slow process, and that the greater the oxygen tension the quicker the restitution, and the greater the supply of intramolecular oxygen available

the more rapid the metabolism. This view can be combined with that of Pflüger, only we must suppose that in the tissues of mammals the restitution of intramolecular oxygen occurs more rapidly and at lower tensions than in those of lower animals. It is very probable that the great difference observed is due chiefly to the difference of temperature. At 37° the processes connected with the absorption and chemical combination of the intramolecular oxygen would doubtless occur more rapidly than at 19°, which is the temperature at which most of Thunberg's experiments were carried out.

Into the question of oxygen absorption in relation to functional activity I do not propose to inquire. We know, for instance, that an active submaxillary gland absorbs oxygen more than three times as fast as a resting gland (Barcroft), an active kidney more than twice as fast as a resting kidney (Barcroft and Brodie), but we are absolutely ignorant of the inner mechanism by which a nervous or chemical stimulus induces an increase of tissue metabolism. In all probability the chemical changes occurring in the tissues of the active glands are of the same character as those in the resting glands, only they take place at a more rapid rate, just as they take place more rapidly at a higher than at a lower temperature.

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BREAD.

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Bread is associated with remarkable commercial and scientific development. Fifty years ago Scotch shepherds, leading a life devoid of the creature comforts of advanced civilisation, carried on their persons raw oatmeal as their "staff of life," principally because it was relatively so cheap. To-day, when oatmeal is 2*d.* per pound, dog biscuits 2½*d.* per pound, and beefsteak 1*s.* per pound, the wheaten bread of commerce is delivered to our doors at prices ranging from 1*d.* to 1½*d.* per pound, according to quality and services rendered by the baker. Out of this small price the baker, the miller, with his elaborate and costly processes of cleaning and milling, the corn merchant, the shipowner bringing wheat from all parts of the globe, the farmer, and the numerous ancillary trades depending on him, have to earn a profit.

No apology for placing commercial considerations in the forefront of an article written for Science Progress is necessary. A rapidly increasing population has wanted bread for food and occupation to earn a living. No country has produced as much food as it can be made to produce. The population of the United Kingdom has increased by 50 per cent. in thirty years. In the early 'seventies we produced about 55 per cent. of the wheat consumed at home; nowadays we are producing only about 20 per cent. It would be interesting, but out of place herein, to inquire whether it would be possible to produce in this country all the wheat we require. The greatest quantity produced here was about 18,000,000 quarters in 1863; we want now in all, say 32,000,000 quarters per annum. A great deal of land then under wheat has been diverted to other purposes, entailing a relatively lower cost of production. The sight of hills in Wiltshire laid out in artificial terraces, covered now by grass, producing indirectly food for man in reduced quantity at lower cost, is suggestive. That is typical of much. If the

self-binding harvester, which rendered possible the growing of wheat in huge areas of virgin lands, had not been invented, or if large ships, some of them able to bring here in one freight at minimum cost as much wheat as many a county produces at one crop, had not been evolved by the progress of science, prices would have been much higher, and wheat-growing would have been commercially possible on soils and under conditions where no man dreams of raising it now. To a miller or a corn-merchant the striking prophecies of Sir William Crookes as to the danger of an absolute scarcity of wheat presented no terrors. He, more fortunate than Frankenstein, laid his own monster by the prospect of increased crops, due to the discovery of a cheap form of nitrogenous manuring. This meant either that the increase in yield per acre would of itself repay the cost of the manure without an increase in the price of grain per quarter, or else that it would be possible to grow increased crops of grain by the aid of fixed atmospheric nitrogen, if a rise in the price of wheat would allow the farmer to buy the manure.

If the former alternative be the correct one—and it is likely to be so—the consumer with an income of say 4*s.* per week per head of his family would have reason to bless the scientist in years to come; but if the latter alternative be the way in which this advantage is to be obtained, even then his fears were not at all formidable. For to the lay mind of a miller or corn-merchant the problem did not seem to be whether the world could grow enough wheat for the actual needs of its inhabitants, but whether it would grow enough at prices equal to 30*s.* per quarter delivered at a British or continental port—two essentially different propositions. At an average of 35*s.* it is certain that more land would be placed under wheat; still more at 40*s.*, much more at 45*s.*, very much more at 50*s.* Price is then a most essential point to be borne in mind by the scientist as well as by the practical man—indeed, the triumphs of science in connection with bread are mostly connected with it. To scratch virgin and fertile soils and produce from eight to twenty bushels of wheat per acre in the new countries of the world, when the average yield in England is over thirty bushels per acre, may be good business, but the scientific attainment does not appear to be striking. Indeed, though a great deal of valuable scientific work concerning wheat, flour, and bread

is being done in these new countries, the most important scientific progress already made concerns the transit of the produce to the markets of the world, the development of railways and ships, the development of processes enabling the miller to clean the produce of slovenly farming, and the joint efforts of miller, baker, and yeast manufacturer in the production from the many wheats supplied to us, differing greatly between themselves and from those which were available thirty years ago, of good bread at the extraordinarily but beneficently low prices now current. But though the most strikingly important scientific developments in connection with our bread supply concern mechanics, and lie in what may be described as the outer circle of its relationship, much important work has been done in the inner circle, and I want in this article to deal with the developments which are closely connected with bread itself.

Wheat and rye are the only cereals used for bread-making. The quantity of rye produced in Europe annually is approximately equal to that of wheat, and it is a fact worth mentioning that the growing of rye is confined almost exclusively to Europe. Indeed, the only countries in which a large rye crop is raised annually are Austria-Hungary, where it equals about two-thirds of the wheat crop, Russia, where twice as much rye is raised as wheat, and Germany, where the proportions are approximately twenty-five of rye to ten of wheat. Analyses stated in generic terms, such as starch, ash, and albuminoids, do not disclose the reason why barley, oats, and maize are quite unsuitable for bread-making, and why rye is relatively unsuitable in British estimation for it. The brewer or distiller knows quite well that any of these cereals can be fermented: their percentages of natural sugar indicate that clearly enough, and bread-making, as ordinarily practised, depends upon the production of gas by fermentation. If therefore the power of yielding gas by fermentation were the only index of bread-making capacity, any of these cereals would be suitable, but the fact that they are not so discloses at the outset a characteristic which is as important as, probably more important than, the power of yielding gas, and that is the power of retaining it within the dough when by fermentation it has been produced, so that the dough can be aerated and made when baked into the appetising and digestible breads of commerce. Doughs made from the flours of barley, oats, and maize do not possess the

power of retaining gas, and as a consequence are quite unsuitable for bread-making. Dough made from rye-flour possesses that power to only a limited extent, and accordingly occupies an intermediate position as an article suitable for bread-making. The difference between wheat and the other cereals in this gas-retaining power is generally ascribed to the fact that wheat contains gluten and the others do not, but Fleurent, as the result of two series of analyses quoted by Bruyning,[1] gives the percentages of gluten in rye, maize, and barley as higher than that of wheat. The percentages of gluten are not the same in various samples of the same cereal, and the one I am about to quote is much lower than the average of flour made from really strong wheats, but the table shows at a glance that the essential difference between the cereals lies in the percentage of gliadin which the gluten contains:

	Gluten in the flour, per cent.	The total gluten contains: Gliadin, per cent., and Glutenin, per cent.	
Rye . .	8·26	8·14	92·83
Maize . .	10·63	47·50	52·50
Rice . .	7·86	14·31	85·70
Barley . .	13·82	15·60	84·40
Buckwheat .	7·26	13·08	86·92
Wheat . .	7·47	75·25	24·75

The apparent contradiction between those who say, for instance, that barley-flour contains no gluten and the analyses of Fleurent which are here given, arises probably from a difference in the methods of extraction. There is no necessity to account with certainty for the apparent contradiction; the essential points for present purposes are that wheat and rye are the only cereals used extensively for bread-making because the others are quite unsuitable, that their suitability or unsuitability depends upon their power to retain gas made in fermentation, and that this depends upon the presence in the flour of a substantial percentage of gliadin, a nitrogenous body of a sticky nature which when wetted becomes figuratively the cement in the concrete formed by the union of the two sister nitrogenous bodies gliadin and glutenin. For several years it was believed that the strength of flour depended on the ratio of gliadin to glutenin in the gluten, but though the presence of a large proportion of gliadin in the gluten is essential, the idea that variations in the relative strengths of flours were

[1] *La Valeur boulangère du Froment*, p. 67.

correlated with or depended upon the ratio of gliadin to glutenin therein has in recent years been proved to be fallacious. It was a most ingenious idea which would have minimised most materially the troubles of investigators, but it had to go the way of hasty conclusions based on work too restricted in purview.

In an article written for a British magazine purporting to deal with modern developments concerning bread or bread-making in Great Britain, nothing more need be said about rye bread, for the quantity consumed in this country is exceedingly small. Practically all British bread is made from wheaten flour. Old men tell us that in their youth, when bread was dear and wages low, some of the best of wheaten offal (the generic technical name for the by-products, consisting principally of husk, made in flour-milling) was used in times of scarcity for the making of common bread, or for mixing with the more costly flour with that object; but since food has become cheap, and wages in amount and purchasing power so much higher, the working classes, who are the large bread consumers, have become particular, almost fastidious, as to the quality of the bread they buy, so that, judged by its appearance, flavour, digestibility, and food-value, modern bread is much superior to that which was in common use fifty or sixty years ago. There is a type of mind possessed by a large proportion of old people which lingers affectionately on days gone by and believes that many old things, including the bread made fifty years ago, were altogether superior to modern ones, and it is useless, perhaps cruel, to argue with such people, or to suggest that in those days they were healthy youngsters, with corresponding appetites, teeth, digestion, and habits, instead of valetudinarians or people satiated with good things. It is obviously impossible to produce now for actual comparison typical bread made fifty years ago, but enough is known to spoil the pretty picture which such a memory conjures up of the beautiful bread made half a century ago.

In a recent political controversy one heard of bread eaten with a spoon in those good old days, and though no one suggests that that was typical of all bread, or most bread, made in those days, specimens made from common English wheats damaged in the wet harvests of 1879 or 1902 came as reminders of what we might have to endure if we were now,

as then, practically dependent on common wheats grown in our variable climate under extremely unfavourable conditions. They used to hear of alum in bread, and we do not, for the modern methods of curing inherent defects in our wheats by blending them with other sorts of different constitution, and modern methods of milling and baking, have come to the rescue and have made quite unnecessary the recourse to that injurious but effective remedy for damaged flours. Another remedy for bad quality in wheat which one no longer finds in use was the admixture of beans. In bad seasons millers used to grind old beans, and mix the flour with that made from wheat, so as to improve their product in the estimation of the baker. In Great Britain that is no longer necessary or desirable, and is not resorted to in any degree, although it is said to be done quite openly in some parts of the Continent. We are told that modern songs are not nearly so good as the old ones, but the critic of modernity appears to forget that he is pitting the average of modern work, good, bad, and indifferent, against the survivals of older times, and a great deal of grumbling at modern bread is done in the same way. Fifty years ago the very best was very good, the average was poor, the bad very bad. In these modern days we have eliminated the very bad—no one would buy it—and under the pressure of competition have learned to make use of a wide range of qualities in wheat and flour, producing therefrom, at minimum cost, flour and bread of excellent and by comparison uniformly good quality. The best bread to-day is superb, free from adulteration, dirt, and contamination. The progress of scientific knowledge has not only made it possible to produce an article of supreme merit, but has also rendered unnecessary all recourse to adulterants.

The whiteness of modern bread is regarded in different ways by various people. The miller thinks it is largely due to his immensely improved methods of wheat cleaning, whereby absolute dirt and dark fungoid contaminations are more perfectly eliminated than they used to be, and to the comparative perfection of his methods of grinding and separating husk from kernel, whereby he obtains from wheat a flour consisting of practically pure endosperm. The baker thinks he has materially affected the colour of his bread by learning thoroughly the use of modern yeasts and adjusting his methods of bakehouse treat-

ment accordingly, to secure a much nearer approach to pure alcoholic fermentation than he used to do. But there seems to be in existence a sort of person who sees in extreme whiteness an evidence of adulteration, or of some nefarious practice. For that state of mind there is absolutely no excuse. Laws against adulteration are in active operation, and definite charges against bakers of adulteration are unknown. Others again, who peel their apples and oranges, are possessed with the idea that nature means us to eat the husk of wheat, and that in refusing to do so we are failing to use a most valuable source of real nutriment. To such a one the whiteness of modern bread is an evidence of misplaced ingenuity. The idea is based on the supposition that the food-value of any article is indicated by chemical analysis, prior to its consumption. That leaves out of account the limited and variable digestive capacity of the consumer. If, therefore, the aid of the chemist be involved, he must do much more than analyse the food of the human being, and must ascertain the amounts and chemical constitution of the fæces and urine voided before the true food-value of an article can be ascertained. This has been done in a most complete manner at the University of Minnesota under the supervision of Prof. Snyder, so far at least as protein, fat, and carbohydrate constituents are concerned; and the results show conclusively that in the case of every type of wheat used the white flour of commerce yielded more nutriment to the body than wholemeal, or wholemeal less its broadest pieces of bran. Even when the bran was reduced to a fine powder mechanically, its addition to white flour lessened the digestibility of the whole when converted into bread. A good deal of work has been done to ascertain the digestibility of the mineral contents of wheat, but no definite conclusion has been arrived at, though Snyder has said that, "as far as phosphates are concerned, white flour contains sufficient to meet all demands." The miners of South Wales and the North demand and obtain whiter bread than the Londoner, and in the light of these carefully ascertained facts as to the real relative food-values of white and brown bread, this preference for the whitest bread has science as well as practice to back it.

Almost all the bread consumed in Great Britain comes into the category of white bread. The degree of whiteness varies according to price and district, but the flour used in its manu-

facture represents an extraction from the wheats of commerce of say 70 per cent. or less. One noteworthy fact in this connection is the small but almost constant proportion of wheat-meal breads consumed. An exceedingly small number of people eat a little occasionally, and so provide themselves with a pleasant change in diet, perhaps with a mild aperient. Basing an opinion upon the amount of trade done in wheat-meals by millers, I do not think that more than 1 per cent. of the bread consumed in England comes into the class of wheat-meals of various kinds or degrees of fineness. In recent years a demand has been created for germ breads. The best known of these is Hovis. They are not wheat-meal breads. The percentage of germ in wheat—the yellow oily part found at the thick end of a grain of wheat, in which alone, as its name implies, is the germ of future wheat plants—is about 1½ per cent. It contains active ferments, and in its raw state is far better out of flour than in it. It is not difficult to keep it out of flour in milling, but owing to the technical difficulty of separating it free from the husk of the wheat, millers only extract as a separate product say ½ per cent. of the wheat ground. The makers of various germ meals cook it, and so destroy the ferments it contains; and, having done so, mix it with the ordinary flours of commerce in the proportions of say 75 per cent. flour to 25 per cent. cooked germ. The percentages of oil and albuminoids contained in raw germ are high—about 8 per cent. and 27 per cent. respectively—and a human being can digest it satisfactorily; but it is obvious that so long as makers of germ meals or bread use a proportion of germ so very much in excess of that which is extracted in milling, only a very small proportion of the population can be fed on germ bread.

What constitutes good bread? The first essential is a pleasant flavour. It has occasionally a definitely bad flavour. That may arise from the flour used, or from faults in the bake-house. Flour is peculiarly susceptible to taint. Railway trucks which on some previous journey have carried tar or a tarry product have tainted flour through and through; the juxtaposition of paraffin, or even oranges, has caused similar damage. An exceedingly small proportion of musty or mow-burnt corns is fatal to good flavour. An actively bad flavour can also arise from bad or faulty fermentations. Mr. Kirkland, the teacher of Bread-making at the Borough Polytechnic, has described the

characteristic flavours of bread as a battle of flavours distinguishing that from a battle of germs in fermentation.

The baker seeks to set up an alcoholic fermentation, but the lactic ferment lives on the same sort of food; and though under ordinary conditions of baking the alcoholic fermentation has the better chance of thriving, lactic fermentation is almost invariably present to some extent. There may be also a fermentation whereby the alcohol produced in a healthy fermentation may be converted into acetic acid. Other ferments may be present, and if the baker allows, through miscalculations as to the necessary times and temperatures or through other errors, the proper and pleasant effects of alcoholic fermentation to be overcome unduly by the other fermentations present, his bread suffers, and he gets either a tasteless, or a sour, or evil-smelling bread according to the magnitude of his error. Flours from some wheats yield bread which is tasteless, even though the bakehouse treatment given them be correct. Such lack of flavour is usually correlated with a low natural moisture—in other words, such wheats are usually grown in a dry, hot climate; and though it is true that wheats subjected to great heat where the summer rainfall is high or substantial, such as those grown in Hungary and Manitoba, possess a very pleasant flavour, there are exceptions to the rule as to lack of flavour, and one is inclined to look behind the climatic influence for the cause of the characteristic. As a help to healthy fermentation, bakers use to some extract "malt extract." The proportion used is so small that the direct effect on flavour must be nil; yet the actual effect is in some cases substantial. An infinitesimal proportion of diastase has a potent effect on flavour, and I suggest, but do not as yet assert, that the natural flavour of wheaten flour depends to a large extent on its diastatic capacity. If sugar be added to the dough the effect on flavour is practically nil.

Closely associated with flavour in bread is its physical behaviour in the mouth. If it there becomes doughy, its true flavour is obscured; and that is one reason why, if the true flavour of the bread is to be ascertained, it should be eaten one day old, and not soon after it comes out of the oven.

This by an easy transition brings forward one point as to digestibility. Saliva does important work, partly mechanical and partly chemical, in the digestion of food. If bread forms

a doughy mass in the mouth, the saliva cannot be thoroughly mixed with it, and an initial serious hindrance is placed in the way of effective digestion. Flavour is a matter largely of personal likes and dislikes. Some people like stodgy bread, which keeps moist or even damp a long time. A good deal of the so-called old-fashioned farmhouse bread is of this description, the result of using weak flours, or of imperfect aeration, or of both causes combined. It is very much open to doubt whether a person used to high-class modern breads would care to eat this stodgy bread for any length of time, though as a change of diet it may at first be very agreeable; but, however that may be, it cannot be claimed that it is easily digested. For thorough digestion, a well-aerated loaf is essential, and that implies the use of a "strong" flour. There exists a popular fallacy that the use of a strong flour means dry-eating bread, and there is a substratum of truth in the idea; for strong flours will stand a long and severe fermentation. If poor-flavoured bread results, the process of bread-making should be blamed, and not the strong flour. On the contrary, a strong flour, with its concomitant high percentage of natural sugar and its ability to stand a complete but rapid fermentation, can and does produce bread of superb flavour, free from stodginess, well aerated, and thoroughly digestible. The Minnesota experiments already referred to have shown, among other things, that the bread made from a strong flour can be digested quite as thoroughly as bread made from weak flours; so that the consumer is able to secure the full advantage of an increased proportion of nitrogen in his daily bread by the use of strong wheats, for great strength is generally an index of high nitrogen content.

There is no necessity to dwell at any length on the causes of whiteness in bread. The baker by scrupulous cleanliness and careful intelligent attention paid to his bakehouse practice has had an important share in the great and palpable improvement in the appearance of modern bread, but the principal cause of the improvement in this particular lies in the wheats used and in their milling. A white flour which is weak will not make bread of the best appearance. Whiteness in bread is largely a question of optics. A stodgy bread will not appear to be as white or nice as one which is properly vesiculated. A loaf made from a weak white flour will not appear to be as

white as one made from a blend of the weak white flour and a strong flour, even though the latter may as flour be darker than the former. The average blend of flour used to-day is much stronger than that in use fifty years ago, and the improved appearance of bread is in large measure due to that fact. But by far the most important factor in the improvement of colour in bread is the modern mill.

Improved wheat cleaning, wheat conditioning whereby the wheat is put into the best condition for the separation of husk from kernel, diminution in the amount and intensity of friction used in grinding, and improvements in the methods of separating the products of grinding, have in the aggregate wrought a revolution in the methods of milling, so that the flour of to-day is an article very superior to old-fashioned flour, partly because it is really free from dirt, partly because it contains a far smaller proportion of powdered husk than the flours of olden times. We have already seen that powdered husk diminishes the dietetic value of flour.

I have at various points in this article referred to the importance of "strength." Before defining exactly what that means in this connection, it may be desirable to state briefly the most important principles of bread-making. The ingredients of bread ordinarily used are flour, water, salt, and yeast. A large proportion of the bread consumed in Great Britain is made from them, and nothing else. The substitution of milk for the whole or for a portion of the water is sometimes made, but that is not usual in England.

It may at a later stage be necessary to attach more scientific importance to the use of salt in bread-making, but for present purposes that may be regarded as a condiment. Bakers not infrequently use some form of yeast food, for the good and sufficient reason that there is not readily available in many flours enough food for the yeast. Sometimes scalded flour is used for that purpose, sometimes potato flour, or boiled potatoes themselves. The scalding or boiling gelatinises the starch, and though the direct action of yeast on gelatinised starch is very small, a mixture of flour, yeast, and gelatinised starch by the complicated effects set up, does in effect provide the yeast with a more effective food than flour itself.

The use of potatoes has, however, greatly diminished, partly because modern yeasts are so much stronger than old ones, and

can more readily obtain their food from wheaten flour; partly because high-class bread is darkened by them; partly because they contain so much natural moisture that their use is not profitable; partly because much more effective and reliable yeast foods have been invented or adopted. Where some form of "yeast food" is wanted, most bakers nowadays use either sugar itself or malt extract. I need not now pause to inquire whether yeast can get its food directly from cane-sugar or whether the hydrolising constituent of yeast has first of all to change cane-sugar into some other form of sugar before yeast can utilise it; but in effect we have in sugar a food which yeast can assimilate, and in malt extract an article which by diastatic action can convert starch into a food for yeast. Only an exceedingly small quantity of either is required—less than 1 per cent. of sugar and say 0·25 per cent. of malt extract, taking the quantity of flour used as the basis of calculation. "Malt diastase" or "absolute diastase" can bring about the same result, and then the infinitesimal proportion of 0·02 per cent. will bring about striking differences in the size, appearance, and flavour of loaves produced from some flours.

Nobody could, or at any rate would, as an article of ordinary diet, eat loaves of the usual shape made from a mixture of flour, salt, and water, and baked soon after the mixture is made. Such a "loaf" made of 2 lb. 2 oz. of dough and baked in a tin would measure say 1,000 c.c. The same ingredients properly fermented and baked in a tin would measure say 2,800 c.c. The difference is due to inflation by gas, mostly carbon dioxide. In the first case, the crust would be so hard that ordinary human teeth could not break it, yet the "crumb" would be practically dough itself, utterly repugnant to the taste, and highly indigestible. Unless such a dough be baked in very thin layers, which the heat could penetrate in baking, it is inedible, and in that form it is no longer bread as modern people understand the term. Aeration is essential. This may be brought about in several ways.

If a mixture of flour, salt, and water be put into a sterilised receptacle, covered up and left under favourable conditions for say thirty hours, one or more forms of fermentation are set up spontaneously. I need not attempt to say what chemical changes have taken place, or what gases have been generated, but the loaves so produced, bad though they may be, are very much

better than those produced from the same mixture baked soon after the mixing is done. Such loaves weighing 2 lb. measure say 1,200 c.c., have a peculiarly sour, but not unpleasant, taste, and smell like cake. A man travelling in the bush would find this form of fermentation very much better than none at all.

There have been many attempts to obtain a satisfactory aeration of loaves without the use of yeast. Yeast itself is not inexpensive, and there is this further point about its use which adds to the expense. When "sown" in a favourable "soil" the plant grows amazingly, and yields as a result of its growth the gas carbon dioxide, the best of known bread aerators, and alcohol. But "out of nothing nothing comes," and the yeast lives on the "soil" or, to be precise, on those elements of the "soil" which it can assimilate. This means that the yeast absorbs and converts into those products, the greater part of which is lost to the baker, a substantial proportion of the flour, say 2 per cent.—a large amount in the course of a year. But none of the substitutes for yeast are satisfactory, though they do not use up for bread-making purposes any of the flour itself. One gas-producing combination used was hydrochloric acid and bicarbonate of soda, yielding carbon dioxide, the good aerator, and salt, the necessary condiment. But the process is bad for two principal reasons: one, that commercial hydrochloric acid often contains arsenic; the other, that the gas generated is evolved very rapidly—so rapidly that the difficulty of retaining it in the dough, always a great one, is very much intensified. The second of these two objections can be raised against any form of baking-powder aeration. To minimise it, small quantities of flour and water can be used; but that provides its own condemnation in the estimation of the baker, and in any case a far larger proportion of the gas generated can be retained by the dough if evolved in the slow and comparatively regular way of yeast fermentation.

The most successful of all the alternative methods of aeration is the Dauglish process, used for the production of aerated bread. Everybody is acquainted with aerated water as a beverage, and the gas which bubbles out of it when an outlet is provided. The essential idea of the Dauglish process, which has been modified in details since its introduction, is the mechanical kneading of the proper proportions of flour, salt, and water under a pressure of from 7 to 14 atmospheres of

carbon dioxide. When the dough so prepared emerges from the kneading machine, it expands because of the gas within it. The whole process is a rapid one, and the difficulty of retaining the gas within the dough is minimised as compared with "baking-powder" methods. But "aerated bread," good though it is, lacks the characteristic and pleasant flavour of first-class yeast-fermented bread. The chemistry of flour and bread is particularly abstruse, and as a layman I am content to say that the complicated actions and reactions resulting from yeast fermentation do cause, when the best of flours and the best methods are used, a particularly pleasant flavour, which aerated bread does not possess. If the alcohol produced has any direct effect, it must be evanescent, for if any at all be left in the bread as it leaves the oven, the proportion is so exceedingly small that it may be regarded as non-existent. Any carbon dioxide that may be left rapidly disappears by diffusion.

For practical purposes yeast holds the field. One important modern development of bread-making is the comparative ease with which high-class yeasts can now be obtained. It is not essential to obtain pure cultures, for the other micro-organisms which exist in commercial yeast can only develop very slightly in dough; but however that may be, modern yeast is a high-class article, produced generally under favourable conditions by specialists and distributed rapidly by our modern wonderful facilities for transport. There can be no doubt that these modern developments are wholly good. In days gone by, some of the fermentations were of the very highest class, but the results were often irregular and poor. A far higher percentage of regularly good results is now obtained. In old literature the term "leaven" is frequently met with. That consists of a portion of dough held over from a previous baking. The fresh fermentation is started by the mixing of the old dough with fresh flour and water, and after an interval the admixture of a little beer yeast and more flour and water. The first batch produced by this method in any day is relatively sour and dark. The advantages of starting an entirely fresh fermentation for each batch of bread are so great that the older method can be said to have been discontinued in England. Formerly bakers used to make their own yeasts from flour, malt, hops, potatoes, sugar, and water as the principal ingredients, but the comparative disuse of the term "barm" indicates that that way of making yeast

by rule-of-thumb methods has given place to the modern scientific ones. Brewers' barm has also been discarded. Bakers say that since brewers began to use substitutes for malt and hops, their barm has become too unreliable for regular use. Whether that be strictly true or whether the modern specialised manufacture of yeast has provided an article relatively better need not be discussed. As a matter of fact, compressed distillers' yeast has almost entirely ousted the other forms of yeast. The effects of present importance may be summarised in the statements that the processes of bread-making have been very much shortened; that modern fermentations approximate more nearly to the desirable pure alcoholic fermentation than olden ones; that it is possible in a large proportion of cases to use flour, salt, water, and yeast only, dispensing thereby with the use of potatoes and other forms of non-farinaceous yeast food, and that as a consequence bread is less likely to be sour or discoloured by undesirable causes than it ever was.

One absolute essential for the production of good bread is the use of good flour. It must of course be pure and free from all dirt and contamination—"that goes without saying"—and modern flour complies with those requirements. It should also contain a sufficiency of food available for the yeast plant, and be able to retain when made into dough a large proportion of the gas into which some of its own constituents have been changed by the action of the yeast. The possession of those characteristics mainly constitutes "strength." The loaves produced from such flour are large, and therefore well aerated, probably shapely, and relatively digestible.

In the April number of *The Journal of Agricultural Science* there is a most valuable and interesting article by Prof. T. B. Wood, of Cambridge. He has shown from experiments on a considerable number of flours, each produced from a single sort of wheat, that "the size of the loaf depends in the first instance on the amount of sugar contained in the flour together with that formed in the dough by diastatic action." In his summary he also says:

It is suggested therefore that the difference between strong and weak flours is connected rather with the physical properties of their gluten than with the chemical composition. Since it is well known that the physical properties of proteids are profoundly affected by small quantities of acids, alkalis, and salts, the

amounts of these substances in strong and weak flours were determined. In the few cases examined it was found that strength was associated with a high ratio of proteids to salts, and weakness with a low ratio. It is suggested that the variation of this ratio may be the explanation of the different physical behaviour of the gluten of strong and weak flours, and that this is the factor which determines that component of strength which governs the shape of the loaf, and its power of retaining gas. This point is receiving further investigation.

This, the latest of all suggestions as to the cause of strength in wheaten flour, seems by far the most feasible put forward. Comparatively recent work has shown that the possession of a good or even of a high nitrogen content is not of itself a certain indication of strength, and the quality of gluten measured by the ratio of gliadin to glutenin is no indication whatever of strength. As a consequence chemists have seemed to be unable to account correctly in terms of their own science for that characteristic of strength which adds so much to the commercial and dietetic value of certain wheats; and if Prof. Wood can show a definite connection between the percentage of fermentable matter in wheat, the percentage of glutenous matter, and the effect on its gas-retaining capacity of its varying percentages of acids, alkalis, and salts, he will have done that which has baffled many chemists the whole world over for many years. By the time this article is published the subject of strength in wheat, more particularly its bearing on the culture of strong wheats in England, will have been discussed at the Leicester meeting of the British Association. Let us hope that by then this hopeful suggestion may have been transformed into definite assertion.

THE LAW OF THE MINIMUM IN THE SEA

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Two methods of research developed during the last twenty years by the German and Scandinavian marine biologists are now affording results of very great interest. One of these lines of research is the investigation of the relations between the nature and abundance of the floating microscopic life of the sea, the *plankton*, and the physical changes that take place in the water from time to time; and the other is the quantitative investigation of the fauna and flora of the sea. The validity of both of these methods of investigation is still, to some extent, a matter of controversy—that is to say, some marine biologists doubt whether we can associate together, with any degree of certainty, the physical changes that take place in the sea with the nature of the plankton; while others argue that, because of the apparently fortuitous distribution of life in the sea, it is impracticable to attempt any estimate of the absolute abundance of organisms in the open water, or on the sea bottom. Certainly neither of the two methods to which I have referred is yet thoroughly developed, and certainly both will be greatly improved. But, nevertheless, each has produced results which have enormously stimulated investigation in other directions.

P. T. Cleve, of Upsala, and Otto Pettersson, of Stockholm, were the first to attempt to correlate the composition of the plankton with the physical condition of the sea. It had long been known that the waters of the seas of Northern Europe were derived in the main from two sources—the Equatorial current circulation of the tropical Atlantic and the southerly flowing Arctic streams. Cleve[1] described a number of "plankton-types" which were characteristic of these main

[1] *Treatise on the Phytoplankton of the Atlantic and its Tributaries*, Upsala, 1897.

streams and their offshoots, as well as others which were characteristic of water of mixed nature, or of water which was normally present in the shallow seas and was characterised by the presence of "Neritic" plankton forms. Other biologists in Norway and Sweden followed up this line of research, and there is now a very copious literature on the subject. Victor Hensen,[1] of the University of Kiel, was the first to attempt an estimate of the abundance of living organisms in a definite sea volume, and he was followed by Brandt, Apstein, and others. Hensen recognised the impossibility of attempting to estimate the numbers of animals living on the sea-bottom or swimming freely through the water, and therefore he devised apparatus by means of which he estimated the abundance of the planktonic organisms. These latter are microscopic in size, and as they float passively about in the sea it was possible to construct and use nets which could be lowered to the sea-bottom and then hauled up again so as to filter a known volume of water. In this way it became possible to estimate the absolute numbers of the organisms exceeding a certain limit of size which were present in the area investigated. Now it should be noted that the primary objects of both of these methods of investigation were different from those latterly contemplated. Cleve and Pettersson attempted to determine the origin of the water which was present in the sea off the shores of the countries surrounding the Baltic. It was known that the climate of these countries depended very greatly on the temperature of the sea, and it was thought that by tracing the origin of the water currents reaching the shores of the Baltic it might be possible to obtain information which would be of value for the forecasting of the seasons. The place of origin of the currents could be determined by a study of the plankton forms—the diatoms chiefly—contained in the sea, and this was the object of the study of plankton-types. Hensen's object in attempting the numerical estimation of the individuals of the plankton was to ascertain what was the absolute number of the useful fishes inhabiting a large area, such as the North Sea. It is theoretically possible to determine this by estimating the number of fish eggs present in the area investigated during the spawning season of the fishes in question, for we know

[1] "Ü. d. Bestimmung des Planktons," Ber. 5, *Komm. Wiss. Untersuch. Deutschen Meere*, Berlin, 1887.

what is the average number of eggs spawned by a mature female fish, and thus the number of the latter which had spawned the eggs counted could be calculated. Now these were the primary objects of the Scandinavian and German plankton investigations, but as the methods elaborated for the solution of the problems were developed other questions of more theoretical interest became studied, and it is some of these which I propose to discuss.

In 1889 the first expedition which had for its primary object the study of the plankton of a large sea area was organised. In that year the *National* left Kiel for a four months' cruise in the Atlantic Ocean. In the course of this famous voyage five traverses of the North Atlantic were made, and quantitative and qualitative plankton collections were obtained from about four hundred stations on these lines. An enormous bulk of material was thus collected, and as the most of this had to be quantitatively examined it is the case that the complete results of the Plankton Expedition are not yet published. Nevertheless, many of the groups of organisms collected are already described, and notable additions to our knowledge of species and of limits of distribution have been made. The first solid contribution to our knowledge of the bacterial flora of the sea, for instance, is contained in the *Ergebnisse* of the Plankton Expedition.[1] The main interest of the voyage, from our present point of view, is that it for the first time directed attention to the cause of the astonishing contrast which has been observed in the distribution of life on the surface of the land and in the sea. The examination of the material collected by the *National* showed that the plankton of the colder parts of the area investigated was everywhere more abundant than in the warmer sea areas traversed.

There is such a profound difference between the distribution of life on the land and in the sea that one fails at first to be convinced of the accuracy of this result of the Plankton Expedition. Everywhere on the land both vegetable and animal life is most abundant in the tropics and decreases as we pass from the equator to the poles. "He who," says Brandt, "has been compelled to force his way through a tropical forest and then sees the stunted vegetation of Spitzbergen just

[1] Fischer, "Bakterien des Meeres," *Ergebn. Plankt.-Exped.* Bd. 4, Kiel u. Leipzig, 1894.

emerging from the soil, is easily convinced of this contrast."[1] But one so naturally supposes that the distribution of life in the sea is similar to that on the land that it is not easy to be convinced that the opposite is really the case. The sea temperature is highest at the tropics, and the intensity of light is greatest there, so one might conclude that the conditions of life would be more favourable in the equatorial zones. Then everywhere in the tropical seas we find a greater variety of species, and the animal forms are more brilliant in colour and more ornamental in shape; and one unconsciously confuses this variety in form with abundance of individuals. Yet there is no doubt that life in the polar and temperate seas is at least as abundant as in the tropical areas. Wherever the bottom-living invertebrate fauna has been sufficiently investigated we find this to be the case, and some Arctic regions show a bottom fauna which surpasses in abundance of individuals any other region which is known. The polar seas are the chosen haunts of the marine mammalia, and these are the largest animals which exist on the globe. The greatest fisheries are those of the Arctic and temperate seas of higher latitudes: I may give as instances the cod fishery of the sea off the Lofoten Islands; the fisheries round Iceland and in the White Sea; and the fisheries of the North Sea. All this abundance of animal life is also indicative of a corresponding wealth of planktonic life, and all experience shows that this wealth exists. Probably the larger marine algæ are more varied in form and more abundant in the temperate than in the tropical sea, and certainly this is the case with the microscopic plants. In the Antarctic Ocean there are ten and a half million square miles of sea bottom which are covered almost exclusively with the dead shells of diatoms. In both north and south polar seas great masses or "banks" of living diatoms inhabit and discolour the surface of the sea, and fishing operations are sometimes impeded by this rank luxuriance of diatom life. Associated with this abundance of vegetable life is the abundance of the other planktonic forms which feed upon it; thus vast shoals of Pteropods inhabit the north temperate seas and the arctic regions, and it is these that afford the food of the whales

[1] "Stoffwechsel im Meere," *Wiss. Meeresunters. Kiel. Komm.* Bd. 6, Kiel u. Leipzig, 1902.

which abound there. Here and there in the literature of the voyages of explorers we meet with the expression of astonishment at the wealth of life contained in the colder seas. Darwin was particularly impressed with the abundance of life in the sea off the coast of Tierra del Fuego—all the more because the land was almost desolate. In those seas the great kelp (*Macrocystis pyrifera*) grows up from a depth of forty-five fathoms at the least, and the thallus of this alga is probably much longer than this. On it is an incredible abundance of invertebrate life, the food of fishes and marine birds. "I can only," says Darwin, "compare these great aquatic forests of the southern hemisphere with the terrestrial ones of the intertropical regions. Yet if in any country a forest was destroyed, I do not believe that so many animals would perish as would here from the destruction of the kelp."[1]

Just the same contrast was observed when the Kiel planktologists made quantitative observations of the abundance of the plankton in the various seas, and these results are all the more significant since they can be expressed numerically. Plankton catches made with the Hensen apparatus showed that the largest catches of diatom life were made in the sea off the north-west shores of Greenland. Nowhere was there such abundance of plankton in the sea as in this area. For several years systematic observations were made in the Baltic in Kiel Bay, and here again large catches of diatoms were made, though not so large as in the Arctic Sea. For comparison with these, catches made in the Mediterranean might be quoted. In these seas the plankton was everywhere less abundant than in the colder Baltic and North Seas; so also with the plankton of the warm Sargasso Sea of the Atlantic Ocean.

What is the cause of this contrast? As we pass from the equator to the poles both the temperature and the intensity of light decrease on the land and in the sea; and we should expect to find a corresponding decrease in the abundance of life if these factors were the only ones to be taken into account. It is true that the extremes are not so far apart in the sea as on the land. The range of temperature on the land is from −66° to about 66° C., but in the sea the range is only from −2·8° to 31° C. The temperature of the sea is therefore more uniform than is that of the land: the change in the intensity

[1] *Voyage of the "Beagle."*

of light is much the same for both. Therefore one might expect that the abundance of life in the seas in the polar regions would not fall off so much as on the land. But so far from this being the case the polar seas actually possess as much life as the equatorial ones, and indeed it is apparently the case that both the marine fauna and flora increase in abundance as we pass from the equator to the frigid zones. Evidently other factors than the distribution of temperature and light must affect the abundance of life. What are they? "One stands," says Kjellmann, "as before an insoluble problem, when he obtains a luxuriant vegetation from the depths of the sea, and this when the temperature of the air is extremely low; when the surface of the sea is covered with a thick sheet of ice; and when nocturnal gloom prevails, even at noonday."[1]

The cause can only be that some indispensable foodstuff of the plants is more abundant in the colder seas than in the warmer ones. We need only consider the plants, for it is only these organisms that can form living substance from inorganic materials, and we know that the animals can only utilise as food the organic substance of other living things. Now what is this substance which is less abundant in the tropical and warmer seas than in the colder ones? Although a plant may require a number of foodstuffs for its maintenance and propagation, yet it does not matter in what proportion the most of these are present so long as one of them is absent or is present in minimum quantity. If this one indispensable foodstuff is absent then the production ceases, and if it is present in small amount then the production is also small. We may compare the "Law of the Minimum" with the strength of a chain which depends on the strength of the weakest link.

Now the "producers of the sea" are chiefly the diatoms, the peridinians and some of the flagellate protozoa, and we are only concerned with the conditions of nutrition of these organisms. They require many foodstuffs, but we may narrow down the inquiry to the three substances—compounds of nitrogen (nitrous and nitric acids and ammonia and the salts of these), silicic acid, and phosphoric acid. Oxygen and carbonic acid are also required, but the former gas is never absent in the sea, and is

[1] Brandt, "Ü. d. Stoffwechsel im Meere," 2 Abhandl. *Wiss. Meeresunt. Kiel. Komm.* Bd. 6, Kiel, 1902.

usually present in saturation amount; while carbonic acid, if it is not present in saturation proportion, is yet as abundant in the sea as in the atmosphere. We have to consider, then, the other substances. Compounds of nitrogen are, of course, essential for all organisms; silica is essential for the formation of the skeletons of the diatoms; and phosphoric is essential for both diatoms and the other organisms, but is required in larger quantity by the peridinians. One of these essential foodstuffs probably governs the production of living matter in the sea.

Naturally we think first of the compounds of nitrogen. It is well known that the amount of living substance generated in a water area depends on the amount of these salts (up to a certain limit, of course) which enters the water mass. In the German carp ponds, to be found in almost every village, sewage matter is deliberately led into the water, and if the latter is not absolutely poisoned, the more nitrogenous refuse which enters the pond the more carp flesh is produced. So also with the shellfish beds on our own shores. Nowhere do mussels, for instance, flourish so luxuriantly as on a shore which is grossly polluted with sewage. Both in the case of the carp ponds and the mussels, the organic nitrogenous refuse is broken down by bacteria, and the nitric and nitrous acids and ammonia so formed are utilised as food by the diatoms. The latter are eaten by the smaller invertebrates, which in their turn are taken as food by the other animals. Considering the important part played by the compounds of nitrogen in the metabolism of the sea, Brandt came to the conclusion that it was these foodstuffs that were present in minimum proportion.

It was, therefore, necessary to ascertain the proportions in which these inorganic nitrogenous compounds were present in the sea. Now the amount is exceedingly small. Although enormous quantities are brought down to the sea by rivers and by electric discharges in the atmosphere, or may be formed from free atmospheric nitrogen by the activity of certain marine bacteria, yet the amount contained in sea-water never exceeds a very small proportion. Because of the minuteness of this proportion, it is exceedingly difficult to estimate exactly the quantity of inorganic nitrogen in the sea. The older determinations are inexact because methods of analysis had not been fully developed, and also because no account had been taken

of the action of bacteria in altering the composition of the nitrogenous compounds in the sea-water samples. The first exhaustive and reliable determinations of the amount of nitrogen compounds in the sea were made by Natterer[1] for the Mediterranean, the Marmora Sea, and the Red Sea. Natterer's work was very exact. He obtained his water samples from all depths; he made the analyses immediately after collection on board the ship; and he used the best methods of analysis that had been developed at the time. Generally speaking he found that nitrous and nitric acids were very scarce in sea-water, so scarce that he found it quite impossible to express their abundance quantitatively, and only referred to it as relatively high and so on. But ammonia was more abundant, and by the use of Nessler's reagent Natterer was able to determine the proportion in which this substance occurred in sea-water. It was most abundant in the water from the mud at the sea bottom, and least so at the surface. The average values are:

In 87 samples there was	0·0077	mgr.	to	0·06	mgr.	per	litre	of	sea-water.
„ 19	„	„	0·061	„	„ 0·1	„	„	„	
„ 5	„	„	0·012	„	„ 0·15	„	„	„	
„ 1	„	„	0·32	„	per litre of sea-water.				

Therefore the amount of inorganic nitrogen in the relatively warm water of the Mediterranean seas was very small.

Not until 1904 were reliable estimations made of the amount of these substances in the colder waters of the northern seas. In that year the German Fishery Investigation steamer *Poseidon* collected water samples from the North Sea and Baltic during the International Fishery cruises, and these samples were worked out by Raben of Kiel.[2] All precautions which previous experience had shown to be necessary were observed by Raben, and his work appears to be quite unexceptionable. The water was filtered to eliminate planktonic organisms, and was sterilised by the addition of mercuric chloride. A critical examination of the known methods of determination of nitrogen compounds in small quantity was made, and Raben estimated the nitrous and nitric acids and the ammonia separately. The sample was

[1] "Chemische Untersuchungen in östlichen Mittelmeeres," etc., *Ber. d. Comm. Erforsch. d. Ostl. Mittelmeeres*, in *Denckschr. Akad. Wien*, Bd. 56, 60–2, 65, 1892–8.

[2] "Quantitative Bestimmung von Stickstoffverbindungen in Meerwasser," *Wiss. Meeresunters. Kiel. Komm.* Bd. 8, 1905.

acidified with acetic acid, and the nitrous acid was distilled off and estimated by the metaphenylene-diamine sulphuric acid reaction. Then magnesium oxide was added to the residue, and the ammonia set free was distilled off and estimated by Nessler's reagent. To the residue in the distilling flask magnesium ribbon was added to precipitate the mercury, and the nitric acid was reduced by means of sodium amalgam and distilled off and estimated as ammonia.

Raben's results were:

One litre of sea-water from the Baltic contained in 1904:

Month.	No. of Samples.	N as NH_3.	N as N_2O_3 and N_2O_5.
February.	13	0·068	0·199 mgr.
May.	13	0·065	0·170 „
August.	13	0·057	0·095 „
From the North Sea:			
February.	12	0·063	0·216 „
May.	15	0·065	0·217 „
August.	13	0·061	0·079 „

Now the above results show that the average amount of nitrogen compounds in Baltic and North Sea water may be taken as about 0·2 mgr. in a litre, or 0·2 parts in one million. It is also of importance to note that the amount is at a minimum in August—that is, in the hottest month in the year.

Nitrogen compounds are thus less abundant in the warm seas of the Mediterranean area than in the much colder seas of Northern Europe, and they are also less abundant in the latter seas during the month when the temperature is highest. Obviously there is some kind of relationship between the temperature of sea-water and the amount of nitrogen compounds it contains.

So much for these compounds, but we have also to consider the phosphoric and silicic acids. The occurrence of both has been investigated by Schmidt,[1] who examined the water of both warm and cold seas. The average amount of calcium phosphate found in the Arctic and Norwegian Seas was 13·8 parts in one million of sea-water. For the Indian and Chinese Seas the amount was 3·5 parts in one million. The temperature of

[1] See Brandt, "Stoffwechsel im Meeres," *Wiss. Meeresunters. Kiel. Komm.* Bd. 6, 1902.

the former area was 7·2° C. to 11·3° C., and that of the latter 22·1° C. to 29·4° C. The warmer seas were, therefore, richer in phosphoric acid than were the colder ones — a distribution which, assuming Schmidt's results to be reliable, is not easily explained. The difference in the temperature is not by itself sufficient, though it is of course possible that there is more carbonic acid in the colder seas than in the warmer; and since phosphoric acid is more soluble in water containing an excess of this gas, it may be that the difference is thus indirectly due to the difference in temperature. Phosphoric acid is also more soluble in water containing a high proportion of dissolved salt than in weakly saline water; but, again, it is not likely that the differences in the salinity of the sea are sufficiently great to account for the variation in the contents in calcium phosphate.

It is, however, probable that Schmidt's analyses were defective. Quite lately Raben made a number of determinations of the amount of phosphoric acid in the water of the Baltic Sea, and found that the amount was much less than was supposed from the results of the earlier analyses. Raben's results are not yet published, but Brandt quotes some of them,[1] and it would appear that the amount of P_2O_5 in these waters varied from 0·14 to 0·25 parts per million in February and May, and might amount to about 1·4 per million in the autumn.

Silica is the third important foodstuff in the sea so far as the plankton is concerned, and the determination of the proportion in which this substance occurs in the sea is of the utmost significance for an understanding of the conditions under which the production of living matter is carried on. Most of the older analyses are of little value, and the only results which are likely to be accurate are those of the analyses made by Raben in 1902–4. Silicic acid can only be determined by converting it into an insoluble form, and when minute quantities of this substance are associated with large quantities of soluble salts the determination is a matter of great difficulty. Raben evaporated 3 litres of the water sample to dryness in a platinum basin, after most careful filtration, so as to remove the diatoms which would obviously give high results if they were allowed to remain in the sample examined. The residue in the basin was then drenched with hydrochloric acid and then

[1] Brandt, *Rapports et Procès-Verbaux, Conseil Permanent International, Exploration de la Mer*, vol. iii.

again evaporated to dryness, and this procedure was repeated three times. Then the solid mass obtained was broken up and acidified with hydrochloric acid, dissolved in water, filtered, and the insoluble residue ignited in a platinum crucible. The insoluble residue was weighed and regarded as silicic acid. But if it had any trace of colour it was wetted with sulphuric acid and hydrofluoric acid was added, the mixture heated, when the silica was expelled as silicon tetrafluoride. Ammonium carbonate was then added so as to get rid of the traces of sulphuric acid on further ignition, and the residue again weighed and the weight deducted from the first weight. In this way Raben obtained what we must regard as the most probable values for the amounts of silica contained in the sea. These results are:[1]

Milligrammes of SiO_2 present in the water of the Baltic per litre (equal to parts per million):

1902, August	(4 analyses)	1·037		1903, November	(6 analyses)	1·084
November	(3 „)	1·26		1904, February	(6 „)	1·015
1903, February	(2 „)	1·45		May	(2 „)	0·655
May	(1 „)	0·65		August	(2 „)	0·926
August	(1 „)	0·93				

Thus the amount of silicic acid in the sea is extremely small, but it should be noticed that there is a well-marked seasonal variation which is exhibited in each of the three years studied.

Now it is evident that there are at least three things (compounds of nitrogen, silicic acid, and phosphoric acid) in the waters of the sea which are present in extremely small quantity, and each of which is essential for the growth of the plankton. If one of these is present in greatly reduced proportion, then it is evident that the production of organic matter by the plants of the plankton, and so by all other organisms in the sea, must be correspondingly reduced. Which of these is it that governs the production? Reasoning only from a knowledge of the older analyses of Schmidt, Brandt came to the conclusion that it was the inorganic compounds of nitrogen that were so instrumental. Taking the case of phosphoric acid first of all, he had no difficulty in showing that more phosphoric acid was contained in the sea than nitrogen compounds, but that much more of the latter were required by the organisms of the plankton. The

[1] Raben, *loc. cit.* Anhang, *Quantitative Bestimmung der im Meerwasser gelosten Kieselsaure.*

amounts of the various foodstuffs required by the plants (and the equivocal organisms with a plant-like mode of nutrition) are in the same ratio as the amounts of those substances which are contained in their dry substance. Now Brandt showed from his analyses of plankton catches that diatoms contain, on the average, about 1·8 per cent. of nitrogen in their dry substance, and peridinians (the next commonest organisms in the sea which feed like plants) about 2·08 per cent. of nitrogen, also in their dry substance.[1] But Knop[2] gives only 0·3 per cent. of phosphoric acid in the dry substance of marine algæ, and this is probably not far from the amount which is also contained in the diatoms and peridinians. Therefore these organisms require more nitrogen than phosphorus, but there was apparently more of the latter element in the sea in an easily assimilable form. The obvious conclusion is, that the calcium phosphate in the sea is not the substance which governs the production.

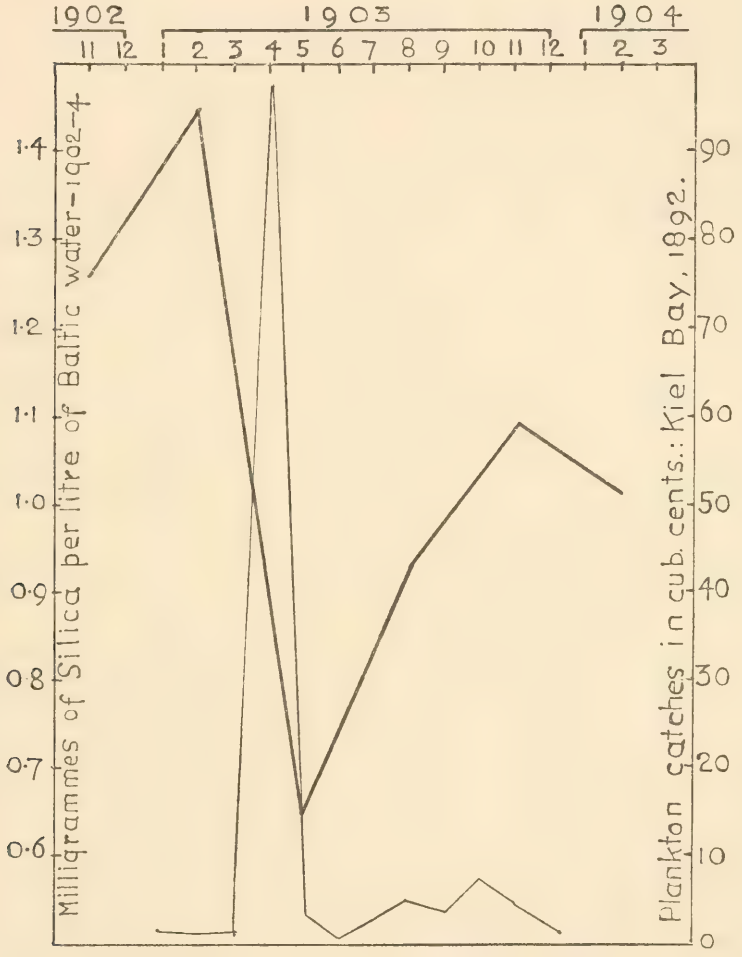
But Raben's later and more exact determinations of the amount of phosphoric acid in the waters of the Baltic compelled a reconsideration of this view. It has been clearly shown, by the quantitative plankton investigations of the Kiel biologists, that there are very well-marked periods of maximum propagation of the various protozoa and protophyta of the plankton. Thus diatoms are certainly at a maximum during March and April, and peridinians are at a maximum in the autumn. Now it is in the latter season that the phosphoric acid is at a maximum of abundance in solution in the sea. Remembering that according to the results of Raben the amount of this substance in the sea is less than was formerly supposed, we see that it is possible that the phosphoric acid may accumulate during the early part of the year, and that, when it has attained its maximum, then the peridinians begin to multiply in increased numbers, so as to cause them to assume their predominance in the autumn plankton.

So also with the silica, only the seasonal fluctuation of this foodstuff is more clearly indicated by the analyses; and so also the seasonal fluctuation of the diatoms is more clearly shown by the results of the quantitative plankton catches than any other group of organisms in the sea—a result which is to be expected

[1] Brandt, "Beiträge zur Kenntniss d. chemischen Zusammensetzung d. Plankton," *Wiss. Meeresunt. Kiel. Komm.* Bd. 3, 1898.

[2] Knop, *Kreislauf des Stoffes.*

when we consider the overwhelming importance of these organisms in the metabolism of the sea. Now this association of the change of abundance of the diatoms, and the change of abundance of silica in the sea, is so clearly brought out by Raben's analyses that I have expressed the two things in one diagram. In the following figure the thin line indicates the



Variations in the amount of silica in the sea and in the abundance of the plankton.

abundance of plankton in Kiel Bay in 1892. The shape of the curve is the same for every year studied. It indicates the volume of the catch of total plankton obtained by a quantitative net;

and it should be noted that the abundance and extent of variation of the diatoms are so much more considerable than those of other organisms, that the variations in the amount of plankton obtained are due almost entirely to these organisms. Note, then, that there are two maximal periods of reproduction of the diatoms—a principal maximum in April and a secondary maximum in October.

The thick line shows the variation in the amount of silica in the water of the Baltic. This substance is most abundant in February and least so in May. From February to the latter month the amount diminishes very rapidly—just as the abundance of diatoms falls off very rapidly. Then we have a secondary increase in the amount of silica, and also an increase about the same time in the abundance of diatoms. During the winter the amount of silica in the sea has been accumulating, and in the spring, when the increased sunlight affords the stimulus for the increased propagation of vegetable life in the sea, this accumulation of foodstuff is made use of and there is a rapid increase in the mass of vegetable life. But this reduces the proportion of silica, and the minimum values for the amount of the latter are found in May, just after the diatoms have been so abundant. From May to August the silica again accumulates, and we find, about the latter period, that there is usually a second period of diatom abundance.

We can consider the silica, then, as a substance which is sometimes present in the sea in minimal proportion. This is certainly the case during those times in the year when the diatoms are present in maximum abundance. Brandt has estimated the weight of silica which is contained in the sea in the form of the skeletons of diatoms during the time when these organisms are most abundant.[1] In one catch, made in the Bay of Kiel on May 15, 1893, there were 3,173 millions of diatoms (mainly *Chætoceros*). The estimated dry weight of this mass of diatom substance was 0·99 grm., and this contained 0·54 grm. of silica. This catch was contained in a volume of water which was estimated as 1·5 cubic metres. Now it is well known that the quantitative plankton net does not catch all the diatoms which pass through the opening, for a number of these are so small as to slip through the meshes of the silk employed in the construction of the net. Brandt estimated that about one-third

[1] Brandt, "Beitr. Chem. Zusamm. Planktons," *loc. cit.*

of the diatoms were caught in the net. Therefore, the 1·5 cubic metres of water contained about 1·5 grms. of silica in the form of diatoms; that is, the water contained, roughly, about one part in a million of organic silica. Now Raben's results showed that Baltic water contained from 1·45 to 0·65 parts in the million of inorganic silica. Since it is not possible that diatoms can absorb more than a large fraction of the dissolved silica, we must conclude, then, that this substance was present in minimal proportion.

But this was an extraordinarily large catch of diatoms, and although the silica was certainly present in minimal quantity during the period of the year when the diatoms were at their maximum of abundance, it must still be remembered that this period is only a short one, and that at other times in the year the silica may be present in such proportion that it need not necessarily be regarded as minimal in amount. We have, therefore, to consider also the nitrogen compounds, and indeed the problem is a very complex one. One is usually inclined in such discussions as these to emphasise the importance of some one particular factor, and to forget that there are usually many others which must also be taken into account. If, as seems clearly the case, the inorganic nitrates, nitrites, and ammonia are also present in less abundance during the autumn than in the spring, then we have to consider the probability that the abundance of these foodstuffs may also influence the production.

Are the nitrogenous foodstuffs present in the sea in minimal quantity? We can answer this question if we know how much nitrogen is present in the sea in the form of living matter, and if we compare this amount with the amount which is present in the same volume of water as inorganic salts in a dissolved form. That is, the chemical composition of the plankton, as well as that of the sea water, must be determined. Brandt made a number of such determinations of the composition of the plankton taken in a quantitative net in Kiel Bay in 1892 and 1893, and his principal results which bear on this question are as follows: the material collected was washed, so as to get rid of the sea-water, and dried at 100° C., and the nitrogen was determined by the ordinary processes of organic analysis. The percentage of nitrogen in the dry substance varied with the nature of the organisms caught; thus diatoms are poor in albumen, while the naked protozoa are richer. The average

results of three catches of peridinians was 3·28 per cent. of nitrogen in the dry substance; that of two mixed catches 3·16 per cent.; and that of two catches which consisted chiefly of diatoms was 2·11 per cent. Now the amount of water in which these catches were contained could be ascertained from a knowledge of the "filtration capacity" of the net used, from the area of opening of the latter, and from a measurement of the depth to which it was lowered. Thus Brandt[1] estimated that these quantities of nitrogen were contained in one cubic metre of water: in the case of three catches of peridinians 0·031 grm.; in the case of the two mixed catches 0·016 grm.; and in the case of the two catches of diatoms 1·019 grm. Generally speaking, the water in the Bay of Kiel contained from 0·007 to 0·04 grm. of nitrogen in a cubic metre—that is, from 0·007 to 0·04 parts per million.

These values when compared with the analyses of Natterer show that if the plankton of the regions investigated by the latter were as rich as that of Kiel Bay, the nitrogen would certainly be in minimum quantity. Natterer did not investigate the plankton, so that a direct comparison of the organic and inorganic nitrogen in the seas dealt with by him is not possible. But we know that the seas of the Mediterranean area are not so productive as those of the north. It is, however, possible to compare the results obtained for the Kiel seas. According to Raben's analyses the water of the North Sea and the Baltic contains, on the average, not less than 0·2 parts of inorganic nitrogen per million. Now the organic nitrogen present in the same sea area is not less than 0·007, and not more than 0·04 per million. Therefore there is at least four times as much inorganic as organic nitrogen in this water. Is this foodstuff present in minimal proportion? We must remember that not all the compounds of nitrogen which are dissolved in the sea can be assimilated by the marine plants. In the case of a land plant the co-efficient of absorption by the root-hairs is probably only a few per cent., but in the case of the diatoms this co-efficient is certainly much higher, for these live bathed in a solution of the foodstuffs and because of their extremely large surface area when compared with their volume, the co-efficient of absorption is high—probably not less than 50 per cent. It is possible that in the warmer periods of the

[1] Brandt, "Beitr. Chem. Zusamm. Planktons."

year, when the amount of nitrogen compounds in the water is least, this foodstuff is in minimal proportion.

What is the cause of the poverty of the warmer sea areas in inorganic nitrogenous foodstuffs, and that of the relative scarcity of these in the colder seas during the warmer months of the year? It was suggested by Brandt [1] in 1899 that there must be a considerable destruction of nitrogen compounds in the sea, for they are continually being added to the latter by drainage from the land, by electric discharges in the atmosphere, and possibly to some extent by direct fixation of atmospheric elementary nitrogen. The amount of this element which is added to the sea in the course of a year in a large area such as the North Sea and Baltic can be determined approximately, as well as the amount of nitrogen, in the form of food fishes and other animals, which is removed from this sea area in the same period. When these values are compared, it is seen that the nitrogen added to the sea is greatly in excess of that taken from it. Some of the fixed compounds are therefore returned to the atmosphere as elementary nitrogen. Now it has been known for many years that there are bacteria on the land which can break up nitrates, nitrites, and ammonia, and set free the nitrogen in the elementary form. It was also suggested by Vernon [2] in 1898 that such denitrifying bacteria were also present in the sea. But it was not until 1902 that the actual demonstration of the presence and activities of these organisms was made by Baur.[3] Gran [4] also wrote about them in 1902. Then Feitel [5] in 1903 made further investigations on the occurrence and activities of these micro-organisms.

Baur made use of a nutritive solution containing potassium phosphate, magnesium sulphate, calcium chloride, magnesium carbonate, ammonium sulphate, and sodium chloride to the extent that this latter salt is present in the sea-water. This

[1] Brandt, "Ü. d. Stoffwechsel im Meere," *Wiss. Meeresunters. Kiel. Komm.* Bd. 4, Abth. Kiel, 1899.

[2] Vernon, "The Relations between Marine Animals and Vegetable Life," *Mitth. Zool. Stat. Neapel*, Bd. 13, 3 Heft, 1898.

[3] Baur, "u.d. zwei denitrificenden Bakterien aus der Ostsee," *Wiss. Meeresunters. Kiel. Komm.* Bd. 6, Abth. Kiel, 1902.

[4] Gran, "Studien u. Meeresbakterien; I. Reduction von Nitraten u. Nitriten," *Bergens Museums Aarbog*, Bergen, 1902.

[5] Feitel, "Beiträge zur Kenntniss denitrifizender Meeres Bakterien," *Wiss. Meeresunters. Kiel. Komm.* Bd. 7, Abth. Kiel, 1903.

fluid was inoculated with mud from an aquarium which was rich in nitrates and nitrites. A rich bacterial flora developed, and in a few days the solution was free from nitrates.

Baur then inoculated a solution containing fish-broth, peptone, and potassium nitrite with the mixed culture from the former solution, and by suitable methods two new bacteria were isolated from this medium. These he called *Bacterium actinopelte* and *B. lobatum.* The growth of these organisms in pure culture is indicated by the formation of a froth and by the later evolution of gas bubbles which are nitrogen, and finally nitrogen with some nitric oxide. The nitrate and nitrite are broken up into free nitrogen, so that finally the solution becomes free from these compounds, and the metaphenylene-diamine sulphuric acid reaction becomes negative. Both bacteria are aerobes, but they can exercise their denitrifying activities in the absence of oxygen, the latter element being obtained from the nitrite or nitrate decomposed. The moderate access of oxygen, however, stimulates the decomposition of the nitrogen compounds. Both require carbohydrates, and can live apparently in decaying vegetable refuse.[1] Lowered salinity of the sea-water does not seem to affect them, and one of them can live in fresh water, though whether the denitrifying activity can be carried on in the presence of the numerous bacteria of the latter is not clear.

The relation of the denitrifying activity of both of these micro-organisms to temperature is of the very greatest interest. Baur made a series of twenty cultures at different temperatures. At 25° C. froth formation (the evolution of free nitrogen) began about twenty-four hours after the commencement of the experiment, and in a period of seven to eleven days all the nitrite in the solution had been decomposed, the frothing ceased, and the metaphenylene-diamine sulphuric acid reaction was negative. At 15° C. the gas formation began after three or four days, and the nitrite reaction and frothing did not disappear till about twenty-eight days after the commencement of the experiment. At 4·5° C. frothing did not begin until the eighteenth to twenty-second day after the establishment of

[1] Baur found that proteid matter had to be supplied in the form of broth or peptone. Carbohydrates were also necessary. Gran found that denitrifying bacteria might obtain their nitrogen from nitrite and their carbon from organic acids.

the cultures, and after 112 days all the five tubes dealt with still frothed, and the metaphenylene-diamine reaction was positive, showing that there was still nitrite in the solution. Finally, at a temperature of 0° C. no growth and no gas formation was observed, although the cultures were kept for 107 days. These experiments were made with *B. actinopelte* in mixed culture, but pure cultures gave similar results. *B. lobatum* was also experimented with, and much the same behaviour of the micro-organism was observed. It can apparently denitrify at 0° C., but the action is extremely slow.

Here, then, is a possible, perhaps a very probable, explanation of the relative scarcity of nitrogen compounds in the warmer seas and the decrease in the amount of these which has been observed in the colder seas in the warmer months of the year. Denitrifying bacteria such as those mentioned have been shown by Baur and others to be widely distributed, in the Baltic at least, both in the mud at the sea-bottom as well as in the free water. Probably the distribution will be extended very generally to all seas as soon as adequate investigations have been made. Such observations are being carried out on the cruises of the International Fishery Investigations, but the results of these are not yet published. If, as seems to be the case, these bacteria are common in the sea, then a considerable amount of denitrification must go on there. It is true that these organisms require organic matter—carbohydrates or organic acids—in order that they may exercise their function of decomposing nitrogenous salts, and also organic nitrogenous matter as well. They can only act on the latter when it has been nitrified by the nitrifying bacteria which we know are present in the sea. When by their own activity the nitrates, nitrites, and ammonia resulting from the activity of the latter micro-organisms have been reduced, then the denitrifying bacteria are condemned (*verdammte*) to inactivity, but there is always a fresh supply of the latter substances brought down to the sea by rivers, and originated also by the decomposition of the dead bodies of the organisms which die in the sea, so that the process is a continuous one.

The optimum temperature of the denitrifying bacteria hitherto described is from 24° C. to about 28° C. It is of course possible that forms may be described which are able to denitrify at a temperature little above 0° C., but it is unlikely

that such will be discovered. It will at once be obvious that the different behaviour of these organisms with regard to temperature explains why it is that inorganic nitrogenous substances are more abundant in the warmer than in the colder seas. At the temperature which obtains in the former they are able to carry on their work of breaking down nitrates and nitrites, while in the cold waters of the arctic seas, where the temperature may be for many months in the year little, if any, above that of freezing-point of fresh water, the activity of the denitrifying bacteria is inhibited or arrested, with the result that the compounds of nitrogen are allowed to accumulate. In the temperate seas intermediate conditions are encountered.

So the antithesis between the sea and the land with respect to the distribution of life according to temperature is most probably to be explained. Those organisms which exhibit a plant-like mode of nutrition are more abundant in the colder or temperate seas, because they there have a greater amount of foodstuffs at their disposal; and with the abundance of the diatoms, and the organisms with a similar mode of feeding, stands the abundance of the animals which feed directly, or indirectly, on these lower forms of life. There must always be an exact relationship between the producers and the consumers, the latter varying in abundance with the abundance of the former. The scarcity of the ultimate foodstuffs in the warmer seas is due to the greater degree of denitrification that goes on there. We cannot suppose that this same amount of denitrification takes place on the land, and so life in the tropical countries is more abundant than in the cold ones, the more favourable physical conditions of the former being allowed to influence the production unchecked by other inimical factors.

AMERICAN ECONOMIC ENTOMOLOGY

By R. LYDEKKER, F.R.S.

With the practical common-sense characteristic of the nation generally, the Government of the United States was one of the first to recognise the importance of full knowledge of the habits and life-histories of the numerous species of insects, both indigenous and introduced, which infest cultivated crops, orchards, and plantations in such numbers as to constitute more or less serious menaces to the progress, if not to the very existence, of agriculture and horticulture. Of course local conditions have had something to do with the energy displayed by the authorities in this connection, for it cannot be denied that America, with its illimitable area of cultivated land, and climatic conditions varying from the tropical to the arctic, offers facilities for the propagation and spread of insect-life altogether unparalleled in Europe. This, however, in no wise lessens the credit due to the Federal Government for its early recognition of the supreme necessity of fighting insect invasions with all the available resources of science, and the consequent establishment of the Bureau of Entomology as a division of the Department of Agriculture. Nor have the dependencies of the great Western republic been slow to follow in the footsteps of the central Government, as witness the establishment at Honolulu of an experimental entomological station by the Hawaiian Sugar-Planters' Association, which has already done good work, and will doubtless accomplish still more in the near future. In the Philippines also the importance of economic entomology has been fully recognised since those islands came under American sway.

In some manner affiliated to the Bureau of Entomology, there is also the American Association of Economic Entomologists, the reports of whose meetings are published by the official establishment.

The enormous field covered by the work of the Bureau and the Association is very clearly indicated in the report of the

eighteenth annual meeting of the latter body forming Bulletin No. 60 of the Bureau. In this we are reminded that the economic entomologist takes cognisance not only of insects properly so-called, but likewise of spiders and myriapods; while now and then, as in the case of the wood-louse and the pill-millipede, he may be called upon to deal with members of the crustacean class. Something considerably over a million would be only a moderate estimate for the number of species of insects, spiders, and myriapods; and to describe them and their life-histories adequately would require a library of some seven thousand stout octavo volumes. Assuming, however, only one-half of these to be of any economic importance, it is estimated that between three thousand and four thousand similar volumes would be necessary to contain a full account of them, with discussions of their ravages and the remedies required to check the same. Evidently, then, the economic entomologist must be endowed with great powers of application and possessed of a great store of knowledge, in order to be able to grapple effectively with his task; although it is, of course, not to be assumed for a moment that any one man is capable of being a specialist in every part of such a vast subject.

During recent years the field of work of the economic entomologist has been very greatly widened. The connection of insects with human disease, as exemplified by the propagation of malaria by mosquitoes of the genus *Anopheles* and of yellow-fever by those of *Stegomyia*, forms, for instance, a portion of his studies; while the relations of insects to the diseases of plants, and also the fertilising of flowers by insect agency, are likewise subjects which should come within his purview, although too often in the past they have received less attention at his hands than their importance merits. Again, the application of scientific methods to bee-keeping and to silk-worm-rearing is likewise intimately connected with economic entomology in its wider sense.

After all, however, and more especially from a popular point of view, the great and prime work of a bureau of entomology is to check and keep, so far as possible, under control the insect pests which from time to time inflict such grievous injuries on our corn, fruit, garden, cotton, sugar, and other crops, as well as on our forests and our nurseries of young trees and plants. To prevent such "plagues" from rendering the country a desert,

and to use every effort in checking the spread of insects introduced from other countries, are the prime functions of the American Bureau of Entomology. How well it has carried out its gigantic task in a number of cases it is the object of the following notes to illustrate.

Before proceeding to discuss a few selected instances, reference may, however, be made to the summary of the laws in force against injurious insects and foul brood in the different States of the Union forming the subject of Bulletin No. 6 of the Entomological Bureau. The careful and complete manner in which this summary (which was issued in November of last year) has been drawn up enables the reader to ascertain with the least possible trouble how efficacious for their purpose are these laws as a whole, and in what respects they might be improved by additional local legislation.

There are two insects to which, from force of circumstances, the Bureau has been compelled to devote special attention, the first of these being the Mexican cotton-boll weevil, and the second the San José, or Chinese, scale-insect. In both instances the Bureau is to be congratulated on the results of its investigations, both from the scientific and from the practical point of view.

The Mexican cotton-boll weevil (*Anthonomus grandis*) is a relatively small beetle whose larvæ attack the heads or "bolls" of growing cotton, upon the internal tissues of which they feed. The species has been known to science since the year 1843, when it was observed in Vera Cruz; and five years later it made its appearance in one district of Mexico in such numbers as to render cotton-growing impracticable. When or by what means it crossed the Rio Grande it is now impossible to determine. Certain it is that the insect made its appearance in Texas during 1892, and two years later had spread to half a dozen counties in the Bronnsville district, when it was brought to the notice of the Bureau of Entomology as a serious enemy to cotton-growing. An officer of the division was immediately dispatched to Texas to make investigations on the spot. The main practical suggestion contained in his report was that cotton-growing should be prohibited on a belt of land along the Rio Grande. Had this been done, the northern advance of the pest would have been effectually stopped. The authorities in Texas did not, however, at the time see their way to adopting the suggestion; and in

consequence the staying of the plague by this means soon became impracticable. Not to dwell on details, it will suffice to state that by 1903 the pest had spread over almost the whole of Texas, while a few sporadic outbreaks (ultimately traced to direct transport from the affected area) were noticed in Louisiana.

How much damage the weevil did during the first decade of its presence to the cotton crops in Texas is by no means easy to ascertain. Previous to its appearance there had been considerable shortage in the produce, due to drought and other unfavourable climatic conditions; but when once the weevil had made its presence manifest all unsatisfactory results were, as a matter of course, attributed to the pest.

At first it was assumed that cotton-growing would have to be given up in Texas as a result of the visitation; but more sober estimates resolved themselves into the conviction that it would no longer be reasonable to expect that the yield of the country in cotton would double itself in the course of a few years. At a rough estimate, the damage done by the weevil to the cotton crop in Texas up to the year 1903 was put down at about two million sterling. Fears were at this time entertained that equally serious damage would accrue by the spread of the insect to the States east of the Mississippi, but whether these anticipations have been realised we are unaware.

Certain remedial measures—notably the cultivation and introduction of a mite parasitic on the weevil—were suggested in a Farmers' Bulletin issued by the Bureau in 1903; and a year later the authorities felt themselves justified in writing as follows:

"In spite of the general serious outlook, however, it must be stated that fears of the damage the weevil may do are very often much exaggerated, especially in newly invaded regions. It is not at all necessary to abandon cotton. The work of the Division of Entomology for several seasons has demonstrated that a crop can be grown profitably in spite of the boll-weevil, and this experience is duplicated by many planters in Texas."

By 1906 the officers of the Bureau were enabled to write in a still more hopeful strain. In the early stages of the investigation it was observed that weevil-attack is often followed by a decided change in the structure of the tissues constituting the bolls and buds. The interiors of such develop a mass of "proliferating" tissue which tends to close up more or less completely all vacant

spaces; and it is this closing-up process which proves fatal to a certain percentage of the weevil-grubs, as well as to pupæ and adult beetles.

"It seems safe to conclude," runs the text of the Bulletin of 1906, "that the great majority of deaths due to proliferation may be caused by the mechanical effect of the formation in first enveloping the larva so closely as to prevent its movement, and then the continued formation producing sufficient internal pressure slowly but surely to crush to death the foe whose attack has called forth this effort at self-defence on the part of the plant. Such an explanation alone accords with the facts as we know them. These observations present to us in a very vivid way an illustration of the intensity of the struggle going on between plant and insect life. It is a life-and-death struggle, and it is not always the insect that wins," especially, it is added elsewhere, when man is on the side of the plant.

On an average, it is believed that proliferation leads to the death of about 13 per cent. of the weevils. In some cases, however, the percentage rises as high as 30 per cent.; and it will be obvious that great advantage would attend the cultivation of strains of cotton which naturally exhibit a strong tendency to proliferate, or which can be made to do so under the influence of artificial stimulants.

To quote once more from the Bulletin of 1906, the following statement with regard to the actual value of proliferation in keeping the boll-weevil under control will be read with interest:

"From a comparison of the results obtained it was hoped that some factors might be found which could be used practically in increasing proliferation, and thus rendering it more effective as a factor in controlling the weevil. In many cases the results of the work have been quite different from those anticipated, but enough has been learned to justify the assertion that at present proliferation is a more important factor in retarding the multiplication of the weevil than are the parasites which have thus far been found."

The moral of the whole problem is that the most likely methods of keeping the pest under control will be found to consist in a judicious combination of influences inimical to the development of the weevil with those favouring the improvement of the cotton-crop itself.

Even this, however, does not exhaust the case of the cotton-

boll-weevil, for in a Bulletin issued in January of the present year it is pointed out that, after all, the simple expedient of burning the cotton-stubble in autumn will probably be found the most efficient way of keeping the insect in check. It has long been known that a considerable percentage of the beetles die during hibernation, and it will be obvious that if the numbers of those which hibernate are sensibly reduced, the cotton-grower may be said to have a double-edged weapon in his hands.

Quite recently it has been discovered that a Texan ant (*Solenopsis geminata xyloni*) is likely to prove an effective check on the weevil. It seems at home on all kinds of soil, and is doing good service on nearly all the area now infested.

Till the advent of the boll-weevil little count was taken of most of the other kinds of insects by which cotton is attacked in Texas; the crop being of such a rank and free-growing nature that minor local injuries were scarcely worth the expenditure of time and labour. All this has been changed by the weevil, the margin of profit being so reduced that attention must now be paid to the smallest details in order to render cultivation remunerative. The Bureau has therefore devoted a special Bulletin, published in 1906, to the insects other than the weevil which attack cotton in Texas and the best methods of checking their ravages.

We may next turn our attention to the investigations connected with the appearance in the San José Valley, California, of a scale-insect (*Aspidiotus perniciosus*) belonging to the same family (*Coccidæ*) as the cochineal insect. In consequence of the locality where it was first noticed in America, the pest has been very generally called San José scale, although now that its true habitat has been ascertained (thanks to the energy displayed by the Bureau of Entomology) it should be termed the Chinese scale-insect. Except as regards the manufacture of cochineal, the *Coccidæ* have hitherto been regarded as insects of no practical importance and of little general interest. The appearance and spread of the San José pest have, however, utterly changed all this, and scale-insects are creatures of first-class importance and interest in the United States, where the most diligent efforts of the Entomological Bureau have been directed to stop the spread and check the ravages of the pernicious species introduced into California.

Peach-trees imported from China by one James Lick, who in 1871 and 1872 had an estate in the San José Valley, were the means of introducing the pest into the New World. It was not, however, till a special expedition had been dispatched to the Far East that this was definitely ascertained, and the habitat of the mysterious scale definitely located among the mountains of north-eastern China. To the secluded nature of this habitat, and the comparatively few and unfrequented trade routes by which it is traversed, is due, it would seem, the circumstance that the pest had not long ago penetrated into other parts of the world. It is true indeed that at some apparently unknown date it had made its way into Japan (of which it was at first supposed to be a native), but there it stayed without making its unwelcome presence manifest elsewhere.

Athough, as we have seen, introduced only in 1871 or 1872, so early as 1873 the Chinese scale had already become a serious pest in Californian orchards immediately around the estate where it first appeared; and seven years later the damage due to its ravages was enormous, whole orchards of well-established trees in fine bearing condition being more or less completely destroyed. For it is a peculiarity of the visitation that the insignificant-looking little flat horny scales under which the insects undergo their development infest all parts of the infected trees (chiefly apples and oranges), from the stem to the leaves, blossom, and fruit, and thus, if left undisturbed, ultimately lead with almost unerring certainty to their death.

Such a vigorous invader was not likely to be long content with the comparatively narrow limits of California; and slowly but surely the pest crept along the Pacific States till by the early years of the closing decade of last century it had reached the plantations of tropical New Mexico in the one direction and the orchards of temperate British Columbia in the other.

Currant-bushes imported from New Jersey were responsible for the appearance of the dreaded pest in the luxuriant orchards of Virginia in the summer of 1893; and a few years later the insect had invaded most of the eastern United States, while at the present day there seems to be scarcely a county in the Union which is altogether free from its detested presence.

One of the objects of dispatching an expedition to ascertain the native home of the scale-insect was to find out the indigenous species which made the pest their prey, in the hope

that these might be effectual in keeping it under control when introduced into America. After much search and deliberation, a species of ladybird indigenous to North-eastern China was held to be best worth a trial for this purpose, and a number were accordingly transported to the United States. In some parts of the States the colonies of ladybirds thrived and did vigorous execution on the scale-insects; but parasites took to preying upon them, while the use of washes as a means of destroying the pest naturally led to partial or complete starvation of the ladybirds. Attention has accordingly been concentrated on obtaining the most effectual kind of wash, with the result that a sheep-dip, into which lime and sulphur largely enter, has been generally adopted.

The use of this wash has brought the scale-insect to a great extent under control; and fears that fruit-growing would have to be abandoned in many districts owing to its ravages may be said to be practically at an end. Incidentally it has been ascertained that the lime and sulphur wash has a most excellent effect in destroying fungoid growths, so that its use is recommended in the case of trees which show no signs of the scale. Moreover, as in the above-mentioned instance of the cotton-weevil, the presence of the pest has led to much greater care on the part of growers in the matter of selecting, planting, and tending fruit-trees, with the most satisfactory results as regards the general condition of the orchards and the amount of produce they yield.

The third pest to which the Bureau has of late years directed special attention is the gipsy-moth (*Porthetria dispar*), also an introduced species, whose native home is the European continent. Unlike the cotton-weevil and the Chinese scale-insect, the gipsy-moth has at present succeeded in invading only a comparatively small tract of territory, being confined to the eastern districts of Massachusetts, Rhode Island, southern New Hampshire, and a few localities in Connecticut and Maine. The invasion of this insect has raised the question whether it is incumbent on States in which pests of this nature make their appearance to bear all the cost of efforts made for their extermination, or whether this should be shared by the supreme Government at Washington.

Although the gipsy-moth has an extensive range in the Old World, inclusive of a large portion of Asia and North

Africa, in Europe at any rate it is only very occasionally that it appears in numbers sufficient to effect any serious harm. Not so in America, where climatic conditions conduce to its multiplying in an extraordinary degree. The introduction of the species was due to an astronomer residing at Medford, who was making experiments on silk-spinning caterpillars, and in 1869 imported some of those of the gipsy-moth. These were kept on a shrub under netting, but during a gale the net was torn and the full-grown moths escaped. Although notice was given of the escape, the insect was not noticed in the district for several years, although by 1889 it occurred in such numbers as to constitute a real pest.

Medford at first endeavoured to fight the invader alone, but in 1890 the State of Massachusetts furnished financial assistance for the same purpose. This was continued till 1899, when further funds were refused; this state of affairs continuing until 1906, when active efforts were resumed by the State. The interruption of the work of repression and hoped-for extermination may be described as almost disastrous.

"In 1899," it is stated in a recent Bulletin, "the State Board of Agriculture had the problem well in hand, and at that time it seemed very probable to skilled practical entomologists who looked into the matter that even extermination was possible in the course of a comparatively short time. But the five years' interruption of the work caused the spread of the insect from a restricted territory of 359 square miles throughout an extended range of 2,224 square miles."

For a long time the National Government refused to participate in the work of checking the advance, but Congress has recently voted 82,500 dollars for the purpose of checking the further spread of the gipsy and the brown-tailed moth.

As regards the *modus operandi* of this, it became evident after careful investigation that the moth spreads itself by means of vehicles proceeding from the infected territory along the main roads. Accordingly, it was deemed advisable to take effectual methods for keeping these roads in the most thickly infested districts as scrupulously clean as possible. This has been done, but with what results the future must show. As regards the isolated colonies of the moth, attempts have been made to stamp them out of existence, but we must await the end of this summer to see whether these have been really effectual.

One of the most serious injuries caused by this insect is to park-lands in Eastern Massachusetts, where thousands of acres are infested by its countless swarms. So numerous indeed is the pest that the ordinary methods of destruction become almost impracticable owing to the enormous expense of their application. Under these circumstances it is recommended to cut and burn all low covert, as well as refuse generally, and likewise to fell and destroy all old and decayed timber containing cavities suitable for the moths. Efforts are also being made to introduce parasites infesting the species in Europe, in the hope that these may aid in checking its spread in America.

To refer to many of the other lines of investigation carried out by the Bureau would far exceed our limits of space, and it must therefore suffice to allude only to a few of the more interesting cases.

During the year 1880 the south of Louisiana experienced a visitation of the sugar-cane beetle (*Ligurus rugiceps*) of such severity that many planters gave up growing sugar and turned their attention to rice, this being especially the case in the Mississippi valley, north of New Orleans. Further investigation showed that this beetle had done great damage at irregular intervals to both sugar-cane and corn crops from about the year 1856 onwards; the injury being in some instances so great that nearly all the crops were cut down. In 1904 a special study of the beetle and its mode of attack was made, in the hope that this might lead to effectual preventive measures.

In addition to the boll-weevil, Mexico is afflicted with another cotton-pest in the form of a large plant-bug, locally known as the *conchuela*, and scientifically as *Pentatoma ligata*. During an unusually severe visitation which occurred recently, the opportunity was taken of making a thorough investigation of the habits and life-history of this insect, which may quite possibly ere long make its way into Texas.

Among a number of insects inflicting more or less serious injury on garden crops in North America, one of the most generally interesting is the species whose caterpillar is known as the fall army-worm (*Laphigma frugiperda*), so called from the fact that, unlike the true army-worm, it does not usually make its appearance in swarms until the autumn. As a rule, the caterpillar confines its attention to grass, but when, as was the case in the autumn of 1899, it appears in countless myriads,

gardens, orchards, and greenhouses are literally devastated. Almost all kinds of garden and field crops—not even excluding tobacco—were attacked by the "army" of 1899. Investigation showed that this species, again unlike the true army-worm, usually reappears in scarcely diminished numbers in the year following a great visitation. Drastic measures are therefore necessary, and poisoning by arsenic or kerosene has accordingly been recommended as the most effectual means of destroying its legions.

The mention of tobacco in the preceding paragraph recalls the fact that the cultivation of this narcotic constitutes an important industry in parts of the United States. Although indigenous, tobacco (perhaps on account of its essential constituent) is much less subject to the attacks of insects than are many other native American plants, and has no insect pests peculiarly its own; nevertheless, a certain amount of damage is yearly inflicted on this crop by insects, and occasionally the injury becomes serious. Several remedies have been suggested, such as poisoning the seed-beds and spraying the plants themselves with arsenic. Still better, perhaps, is the expedient of growing patches of other solanaceous plants, such as datura, horse-nettle, and nightshade, which will attract the insects while the tobacco is still young, and can subsequently be cut down and destroyed with their infesting parasites.

As an example of the excellent work accomplished by the Bureau in helping to save the remnant of the magnificent timber forests of the United States from destruction by insects, the case may be cited of the Black Hills beetle (*Dendroctonus ponderosus*), a lamellicorn species which drives dendritic tunnels under the bark of pine-trees very similar to those made by an English species in elm timber. This mischievous beetle, which measures about a quarter of an inch in length, ranges through the eastern sections of the Rocky Mountain district from the Black Hills in South Dakota to New Mexico, while to the westward it enters Arizona and Utah.

Four species of valuable pines and spruces are attacked and killed by this beetle, which is estimated to have destroyed between 700 millions and one billion cubic feet of timber in the Black Hills Forest Reserve alone, while it has done incalculable damage in Colorado and New Mexico.

Without particularising the methods which have been

adopted for keeping this pest under control, it may be mentioned that by this means, "under proper management, a forest can be protected at a moderate expenditure, or almost without cost where there is a market for the timber."

Leaving the work of the Central Bureau, attention may be directed for a few moments to the energy and resourcefulness with which investigations in economic entomology have been conducted during the last few years by Americans in Hawaii—the working centre having, as already mentioned, assumed the form of an experimental station founded, and apparently supported, by the Sugar-Planters' Association in Honolulu. For many years past sugar-growing in the Sandwich Islands has been heavily handicapped owing to injuries inflicted on the canes by an insect commonly known as the sugar-cane leaf-hopper, and technically designated *Perkinsiella saccharicida*. The leaf-hoppers, it may be mentioned, belong to the order Hemiptera or Rhynchota, which includes some of the most mischievous insects in the world.

The harmfulness of the Hemiptera, or "plant-bugs," is indeed very largely due to the excessive rapidity of the increase of these insects—an increase so great as to suggest that, were it not for the restraining effects of parasites, these insects would in the course of a few years destroy all the vegetation on the face of the earth.

As regards the leaf-hoppers themselves, they are preyed upon by a large number of insects belonging to numerous orders and families; and at an early stage in the inquiry as to the best means of restraining the ravages of the Hawaiian species, it was recognised that the most promising results were likely to accrue from the introduction and cultivation of one or more parasitic species. Accordingly, arrangements were made for dispatching scientific missions to various parts of the world with the object of obtaining as much observation as possible with respect to such parasitic species. Of these expeditions the Bulletin published at Honolulu (referred to in the list of literature at the close of this article) is the outcome. A better and more exhaustive piece of work has, perhaps, seldom been accomplished, forming as it does a most elaborate account of the various groups of parasites known to infest the leaf-hoppers, together with a *résumé* of the life-history of the hoppers themselves. Furthermore, the notes in regard to the best means of

keeping the parasites in captivity and during transport by sea cannot fail to be of great value.

As it will be unnecessary to follow the authors through the various stages of their investigations, we may turn at once to the parasites finally selected as being those most likely to yield satisfactory results. Two factors were of prime importance in regard to this selection—first, that the species should be one with a wide geographical range in order that it might be likely to withstand the variety of physical conditions to be met with in Hawaii; and, secondly, that it should be endowed with great rapidity of increase so that it might have a fair chance of coping with an insect which had probably reached its average maximum.

The choice fell on parasites which attack the eggs of the hoppers; but there were found to be two types of these egg-parasites so eminently suited for the post that it became a matter of difficulty to decide to which to award the preference.

On the one hand are the tiny little hymenopterous egg-parasites of the genera *Anagrus* and *Paranagrus*, collectively known as myrmarids; while on the other are those of the genus *Oötetrastichus*. The special claims of the myrmarids rest on the fact that in the climate of the Sandwich Islands these insects complete their entire life-cycle in about three weeks, and apparently breed nearly at the same rate throughout the year; while they are likewise mainly parthenogenetic, males being only produced at long intervals. The testrastichid parasites, on the contrary, are comparatively slow breeders, taking at least twice as long as the myrmarids to complete their cycle. In compensation for this slowness is the vastly greater number of eggs produced, probably double that of the myrmarids, and, so far as is known, the purely parthenogenetic reproduction.

"If we judge the effectiveness of the two groups of parasites merely on rate of increase (reckoning the life-cycles as twenty and forty days respectively), and suppose that the myrmarid produces twenty and the tetrastichid forty female young, at the end of six months the latter will have produced 4,096 million descendants, but the myrmarid in the same time will have produced one million more."

Other factors, however, come into play, so that the problem is really more complex. The tetrastichid (*Oötetrastichus*) has, for example, the advantage that each individual is bred at the expense of the whole contents of an egg-chamber of the leaf-

hopper, while only a single egg goes to the nutriment of each myrmarid (*Paranagrus* and *Anagrus*).

When the last report was received the advantage was nevertheless held to lie with one of the two species of *Paranagrus*, which is alone capable of destroying about 50 per cent. of the hopper's eggs. The *Oötetrastichus*, on the other hand, was slowly but surely making headway, so that in course of time it will probably become the most efficient instrument of destruction, although not before the year 1908.

The imported egg-parasites are largely assisted by various native insects which feed on the leaf-hopper, together with a fungus which attacks the latter. Had it not been for these native agencies, it is well-nigh certain that sugar-planting would have ceased to be a Hawaiian industry. As it is, the loss is already estimated at millions of dollars.

If it be asked whether the combined attacks of the parasites, the predaceous insects, and the fungus are now sufficient to prevent serious damage from the leaf-hopper, the reply is that more time must be allowed before a definite answer can be given. A strong hope is, however, expressed in the Bulletin that the combined array of forces will eventually prove sufficient to keep the enemy under control.

Reverting to the Central Bureau at Washington, our final illustration may be directed to emphasising the fact that the destruction of noxious insects is by no means its sole aim and object. On the contrary, efforts are made to put such industries as silkworm-rearing and bee-keeping on a more efficient and scientific basis. An example of work of this nature is afforded by the Bulletin on the rearing of queen bees issued by the Bureau in 1905.

It is held by the best bee-keepers to be essential (if the most is to be made out of the industry) to re-stock all hives annually with new queens; but to a great extent the practice is neglected —at all events, in America. This is due in a large degree to the difficulty and expense usually connected with obtaining a sufficient stock of new queens. The Bureau has, however, succeeded in finding a method whereby they can be raised in any numbers at a comparatively trifling cost, and with very little trouble; and it is therefore hoped that in the near future the practice of raising a sufficiency of queens to re-stock all their hives will become universal among bee-keepers.

From a perusal of this brief survey our readers will, we think, scarcely fail to realise the extreme "thoroughness" which characterises all the work of the Washington Bureau of Economic Entomology and the affiliated associations. No trouble or no expense is considered too great for the objects in view; and that this is the right policy to pursue in matters of this nature is demonstrated by the marked success which has attended most of the Bureau's efforts. Had it not been for these efforts, it is probably quite safe to say that many branches of horticulture and agriculture in the United States and its dependencies would by this time have been literally eaten out of existence by insects.

Without instituting any invidious comparisons as to what has been or what has not been done in this line of work in other countries, it is perfectly legitimate to affirm that the important position assigned by the Government of the United States to economic entomology, and the manner in which the practical work is carried out by the executive staff, afford a brilliant example of energy, perseverance, and efficiency to the world at large.

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A SIMPLE APPARATUS FOR PHOTO-MICROGRAPHY

By N. H. ALCOCK, M.D.

The use of the camera instead of the pen in preparing diagrams of microscopic preparations is gradually becoming more common, in spite of the numerous disadvantages that at first attended the process. Some of these arise from the nature of the method, and cannot be circumvented by the exercise of ingenuity. For example, the photographic plate records only one plane of the object, whereas a practised observer by the aid of the focussing screw can bring several planes into view at once, and so it happens that for some purposes, such as counting the chromosomes in an individual cell, photography is much inferior to simple vision. For other purposes, however, this peculiarity is rather of advantage than otherwise, and the superior accuracy and freedom from bias of the photographic method are bringing it more and more into use. Further, a drawing contains only what the observer sees, while the camera shows everything that is there, whether the observer has noticed it or not, and so forms a much more complete record of the preparation than a simple drawing.

When one attempts to take a photograph through the microscope in the ordinary way, a second set of difficulties occurs, which, while not in any way essential to the process, yet commonly gives rise to much loss of time and trouble. Two of these may be briefly noticed. The first arises from slight tremors of the building, which are communicated to the camera, and when high magnification is employed become very troublesome. This can to a great extent be avoided if the whole apparatus be placed on a concrete pillar, solidly built up from the ground, and passing through the floor of the building in which it is placed without actual contact. But if the Metropolitan Railway passes immediately underneath, as happens in one laboratory in London, or if a line of motor

omnibuses is established in the vicinity, this method no longer serves its purpose, and other means must be sought.

The second set of troubles has quite a different cause, arising from the use of aniline dyes to stain in a selective manner different parts of animal tissues. As happens in ordinary photography, these colours appear to the photographic plate in a different manner from that in which they do to the eye, and to get the best contrast in the negative requires some preliminary experimenting with coloured screens, which may be interesting from an optical standpoint, but which causes much loss of time when what is wanted is merely a photograph of the object under examination.

These difficulties can be avoided if the apparatus is slightly modified in the manner indicated below, and the modifications have been tested by actual work with the photomicrographic apparatus at St. Mary's Hospital for some time.

The camera, of any convenient type (*e.g.* Zeiss or Leitz), was fixed to a solid base-board of 2-in. mahogany, 8 ft. long and 11 in. wide. Underneath this was a second board, 6 ft. by 12 in. by 2 in. To the ends of this were fixed four stout staples, and by means of these the whole apparatus was hung from the ceiling by 20 to 22-gauge copper wire. Other description is unnecessary, beyond saying that it is well to have the base of sufficient stiffness, otherwise the apparatus sags in the middle, and so throws the optical parts out of centre. Further, the supporting wires should not be of too coarse gauge, due regard being had to the weight they have to bear; and it is prudent to have a duplicate set quite loose, so as to support the apparatus if the first set should happen to break by any mischance.

The result of this suspension is twofold. In the first place most of the vibration is taken up by the wires, and even when the building is shaken violently by the trains below, a glass of water on the camera hardly ripples. But a more important effect is that any residual vibration affects all the apparatus on the base-board synchronously, and no one part is displaced relatively to any other, the net result being that even in test photographs of diatoms taken at 1,000 diameters, and in Mr. Fantham's[1] photographs of *Piroplasma Bigeminum* at 1,200 diameters there was no trace of shake.

[1] Fantham, H. B., *Quart. Journ. Micros. Sci.* vol. li. pt. ii. 1907, p. 297. See also Ridewood, W. G., and Fantham, H. B., *loc. cit.* vol. li. pt. i. 1907, p. 81.

The illuminating apparatus used is an optical bench, designed for use with either ordinary or monochromatic light. This was originally designed by Dr. E. H. Spitta for use with the electric arc. His plan was then modified and simplified by Mr. H. G. Plimmer, so as to be available for the Nernst lamp, and it is on this latter model that the present arrangement is founded. The lamp, of one vertical filament, is clamped at one end of the optical bench. An achromatic condenser focusses the image of the filament on an adjustable slit; a collimating lens collects the light from this and emits it in a parallel bundle to a narrow-angle prism, which has a Thorpe's diffraction grating on one surface, transmitting an approximately normal spectrum. This is focussed by a third lens on the substage of the microscope. By rotating the apparatus any part of the spectrum can be employed, and the microscope slide illuminated by light of any desired wave-length with sufficient accuracy for the purpose required.

This can be used in two ways. One can, by taking only the violet end of the spectrum, obtain the highest resolution possible in visual work. But for the purpose of photography this use must generally be subordinated to the necessity of obtaining sufficient contrast in the negative. The latter effect can be obtained without any calculations in a very ready and simple manner by rotating the illuminating apparatus, and at the same time observing the ground glass of the camera. At a certain colour the best contrast for the particular microscopic stain under examination is reached, and as the light is monochromatic the photograph exactly reproduces the visual appearance. The amount of time saved by this simple method will be best appreciated by those who have struggled with the older devices.

The time of exposure is less than one would have supposed, varying from 20 seconds at 100 diameters to about 10—15 minutes at 1,000. It can be shortened if the Nernst filament be placed at the focus of the collimating lens and the slit removed, but this is very seldom worth doing.

Photomicrography is with most people only a means to an end—namely, the production of photographs of the highest quality in the shortest time, and as the apparatus described has been found to fulfil these requirements it is hoped that the description will be found of use to other workers.

INSECTS AND FUNGI

By T. PETCH, B.Sc., B.A.

Mycologist to the Government of Ceylon

The long processions of ants bearing pieces cut from living leaves early attracted the attention of all naturalists who visited South America. These leaf fragments are taken into the nest, and are there used as a substratum for the cultivation of a particular species of fungus which forms the insects' normal food. The question as to their use was raised by Bates in his *Naturalist on the Amazon*. Belt (*The Naturalist in Nicaragua*) suggested that the ants were "mushroom growers and eaters"; and the relationship was worked out in detail by A. Möller about fifteen years ago.

Möller found that the pieces of leaves are cut into small fragments and formed into balls, which are packed in a spongy mass in the nest. Over and through the comb thus made runs the mycelium of a fungus which binds it together. This mycelium bears small tufts of hyphæ with swollen tips—the "kohlrabi" heads—which furnish a supply of food in a more concentrated form than would the normal hyphæ. No other fungus is found in the nest—a fact which makes it evident that intruding species are systematically weeded out. The mycelium bearing the kohlrabi heads was proved to be that of an agaric, *Pholiota gongylophora*, which sometimes grows from the fungus garden and appears on the top of the nest; and it has been generally assumed that the production of these heads is due to "selection" exercised by the insects. The shape of the swollen hypha ends varies in the nests of different species, and the agaric has only been discovered in the case of one of these; but Möller believes that the fungus is the same in all cases, and that the differences observed in the kohlrabi heads are to be explained by differences in the degree of specialisation to which the mycelium has been developed by the insects. When the ants are removed from the nest, the fungus garden develops two forms of mycelia,

which bear conidiophores of different types. These are considered conidial stages of the agaric, and the cultivation is, if this view is correct, a "pure culture" of the fungus.

Since Möller described the habits of the leaf-cutting ants—and demonstrated the truth of Belt's supposition that they cultivated fungi for food—no instance of a similar relation between insects and fungi has been established. There have been, it is true, many references to the occurrence of fungi in the nests or burrows of insects; but until recently none of these had been investigated with any degree of completeness.

Probably the best known, and the oldest, example is the occurrence of fungi in the nests of termites (white ants). Smeathman recorded this in 1781, and all subsequent investigators of termites have mentioned it. Haviland describes several species from Africa, Borneo, and Malaya as "fungus eaters." Yet the idea spreads slowly, and we find that an Indian termite has lately been named *Termes mycophaga*, as though the habit were a recently discovered peculiarity of one species. The multiplicity of references has probably given rise to the idea that the connection between the insects and the fungus has been thoroughly investigated—whereas, in reality, all we know consists of more or less chance observations. Recent researches in Ceylon have shown how close is the parallel to the similar habit of the leaf-cutting ants, and at the same time have thrown some doubt on the conclusions which have generally been deduced from Möller's observations. The facts stated in the sequel refer to the nests of common Ceylon species of Termes: *T. redemanni*, Wasm.; *T. obscuriceps*, Wasm.; *T. ceylonicus*, Wasm.; and a fourth not yet identified.

The Termite Nest

As is well known, a termite nest or hill is usually a more or less conical mound of earth, cemented together by the secretions of the insects. It terminates above in one or more hollow pinnacles or "chimneys," whose bore extends down to the base of the nest. It has, however, not been generally recognised that the nest (in Ceylon species) is as extensive—often more extensive—below ground as above; and in consequence theories which will not bear examination have been advanced as to the use of these chimneys. The nest of *T. redemanni* or *T. obscuriceps* is for a long time entirely under-

ground, and it may then have from six to twelve chimneys; but as the nest is extended and the hill is built, the number of chimneys diminishes until (as a rule) the largest nests have only one. It seems probable that the hill was originally only a means of getting rid of the earth excavated in making subterranean chambers. This would then agree with the similar habit of many true ants, though these do not cement the particles together. At present, the chimneys serve as a permanent scaffold to direct the further additions to the hill, and as a means of exit for the winged (*i.e.* male and female) insects. The workers and soldiers do not leave the nest *viâ* the chimneys. A series of observations has shown that the internal temperature of the hill varies only by a few degrees. The hill is, in fact, a natural hot-house, not a structure scientifically ventilated by means of the chimneys.

In the hill, and in the ground beneath it, are excavated numerous chambers connected with one another and with the chimney shafts by minute galleries, which are only large enough to admit the passage of two or three termites at once; and each chamber (except the small one inhabited by the king and queen) is almost filled by a brown structure which resembles in form a coarse bath sponge. This structure, which may be called the comb, serves the insects at once as a nursery and a living room. The eggs are stored in the lower portion, while the larvæ, workers, and soldiers crowd the upper galleries. The comb consists entirely of wood which has been digested by the termites. It is built up of small balls of excreta cemented together in the same way as the particles of earth which form the hill.

The Fungus Garden

It is at once seen that the comb is hoary with a covering of short fungus hyphæ, and that scattered everywhere over its surface are minute white spheres, each about the size of a pinhead. These spheres are more abundant on the roof and sides of a passage than on the floor. Here we have, as has been always recognised, the termite food which corresponds to the kohlrabi heads of Möller's leaf-cutting ants. This has been established by feeding experiments and dissections, the latter being, as Holtermann pointed out, the only reliable method of determining this point, either in the case of termites

or ants. That the practicability of this determination may be realised, and that subsequent comparisons may be intelligible, it will be necessary to describe the structure of these spheres further. Each is seated on a short stalk of intertwined hyphæ. These hyphæ separate above, and branch repeatedly, ultimately bearing cells of two kinds: those in the interior of the sphere end in a branched system of oblong or oval cells; those on the outside bear less branched chains of spherical cells, while intermediate hyphæ have branches bearing either or both forms. Viewed under a low magnification, the sphere appears to be a cluster of spherical conidia only; but on pressing it under a cover glass, the hyphæ radiate, and make clear the arrangement of the internal oval cells. All the hyphæ spring from the short stalk, and are arranged side by side, with scarcely any interlacing. It is probably incorrect to style these cells "conidia"—they are never shed as true conidia are. One never finds on the comb free conidia or a stalk from which they have fallen. If the spheres are eaten—and there is scarcely any doubt of this—they must be devoured as a whole. Döflein makes the quaint observation that they are "just a mouthful" for the termite.

The whole resembles one of the conidial formations which are included under the head of "moulds," but it differs from most of these in bearing two forms of definitely arranged "conidia." If both forms of "conidia" can be found in termites freshly taken from the nest, it may be assumed that the spheres are eaten as a normal food. Holtermann found them in all forms, Döflein found them in all but the mature workers and soldiers, while I have not succeeded in finding them in the larvæ. The workers and soldiers obtain additional food (*e.g.* wood, dead leaves, and other fungi) during their excursions from the nest—a fact which is at once evident from the difference in the colour of the contents of the intestine of these on the one hand and the larvæ on the other. It has been suggested that the larvæ destined to be sexed insects are fed always on the spheres, while those which become workers and soldiers are transferred at some given stage to another diet; in other words, that the differentiation into workers, soldiers, and winged insects is entirely due to their food. This would seem to require a segregation of each form into particular chambers, some of which were destitute of fungi. This has not been shown

to occur; indeed, though combs without larvæ may be found, there are none without fungi in the nests of the species named. Without such segregation it is difficult to see how blind larvæ could be prevented by blind workers and soldiers from eating what was nearest to them, especially if this had hitherto been their only food. And if the differentiation were due to this cause, we should still have to account for its occurrence in species which do not cultivate fungi.

The Agaric

There is yet a further point of agreement with Möller's discoveries. As soon as conditions are at all favourable—often before any other species appears—an agaric grows from the termite combs and pushes through to the surface, sometimes from a depth of three feet. On digging down to the comb, one finds that it is covered with mycelium (very fragile, owing to partial decay), and that it does not contain any larvæ. The fungus has got the upper hand, and the cultivation has "run to seed." Apparently this occurs whenever the comb reaches a certain stage of decay, and other observations seem to indicate that when this happens the whole comb is re-eaten by the termites. Sometimes more than fifty of these agarics begin to develop from a single comb; but, as a rule, only one succeeds in reaching the surface—the others remain aborted in the chamber, and are subsequently eaten. The agaric is fairly common—indeed, in some districts it is the chief edible species; but it is never found except growing from termite nests. Unfortunately it is a pink-spored species (*Volvaria eurhiza*), and (as is usual in this group) it has not been possible to obtain the germination of the spores. The connection between the spheres and the agaric is therefore only a matter of probability.

The "Weeds"

Is the fungus garden of the termites a "pure culture" of the fungus, or may there be other species in it? From the behaviour of fungus spores which the insects eat with dead leaves and wood, it may be assumed that the comb material is sterilised by its passage through the alimentary canal. How the spores of the agaric are introduced is not yet known. It does not seem probable that they are conveyed from an old to a new nest by the insects, and yet none of the termite fungi have

been found elsewhere. But it cannot be supposed that other fungus spores will not be introduced by the insects in their passage in and out; and indeed we find that one other fungus is always present.

If a comb is removed from the nest, and placed under a bell jar, after clearing out all the termites, the spheres turn yellow and decay, and are succeeded in a few days by white columns of hyphæ, which develop into branched conidial forms of *Xylaria*, ten or more centimetres high. If the termites are left in the comb they eat off all these xylarias as they appear. The experiment may be varied by planting the comb in a pot. In this case, the xylarias do not appear till after about fourteen days, they never grow more than two centimetres high, and in some cases they are preceded by a different conidial *Xylaria*. For a long time these forms could not be found in the nest, though they always grew from combs treated as described; and since under cultivation the complete ascigerous *Xylaria* was never developed, there was just a possibility that, as in Möller's researches, they might be a conidial form of the agaric.

The matter was cleared up somewhat unexpectedly. During the monsoon rains, conidial xylarias appeared in large numbers on small patches in the Botanic Gardens, and were recognised as those which first appear when combs are planted in pots. They were followed in a few days by a *separate* ascigerous form, thus explaining why pot-grown forms never developed into full grown xylarias. Finally, at the end of a week, there appeared the conidial form which always develops on combs under bell glasses. On digging down below these patches deserted termite combs were found beneath each one. There appear from the facts recorded here to be two xylarias in the termite comb; but further observations seem to indicate that they are only forms of one species, *Xylaria nigripes*, Klotzsch.

The results may be briefly summarised as follows:—*Termes redemanni* and *T. obscuriceps* cultivate on their combs a mycelium which bears small spheres of "conidia." This mycelium is that of an agaric, *Volvaria eurhiza*. The cultivation never shows any "weeds" in the nests, but when the comb is taken out—or when it is deserted by the termites—*Xylaria nigripes* grows from it in abundance, proving that its mycelium

must be always present in the comb. The termites must "weed out" all foreign fungi, and *Xylaria nigripes* is the one species which defies their efforts to exterminate it.

The Fungi of Leaf-cutting Ants

The leaf-cutting ants investigated by Möller cut small discs from living leaves and carry them into their nests; there they bite them into small fragments and knead them into balls. These balls form the foundation of the fungus garden, and are fastened together by the hyphæ of the fungus. It is at once evident that there can be no sterilisation of this material, and that fungi of all kinds must be taken in with it. The cultivated fungus is more abundant than that in a termite comb, but it resembles the latter in bearing small white tufts, which are eaten by the ants. But the structure of these tufts shows nothing of the complexity of the termite spheres. Each tuft consists of hyphæ with swollen ends, mixed with other normal hyphæ, and there is no definite arrangement. They show the simplest variation it is possible to get in a fungus hypha. Möller calls these swollen hypha ends "kohlrabi heads."

At rare intervals, an agaric grows in clusters on the top of the fungus garden. The latter is near the surface or is merely covered with dead leaves, and there is therefore no elongation of the stalk or modification of the agaric such as occurs in the termite nest. Möller was able to germinate the spores of this agaric, and to grow from them a mycelium which developed kohlrabi heads, though it may be objected that recurrence of such a simple modification does not necessarily denote identity.

So far the parallel is complete, although all the fungi of the termites are more complex than those of the leaf-cutting ants. A difference apparently arises in the growth of the fungus garden after the ants have been removed, and in the cultures made with the mycelium of the garden. When the fungus garden is enclosed in a glass dish, the kohlrabi tufts collapse, just as the termite spheres do under the same conditions. After a few days a dense growth of hyphæ covers the garden and soon develops conidia; and in a few days more, hyphæ of a different kind appear and develop conidia which differ from the first. Möller regards these two "moulds" as conidial fructifications of the agaric; but the evidence hardly seems to

warrant the assumption. The spores of A in pure culture reproduce A, and the spores of the second form B produce only B—it is not possible to grow A from B, or *vice versâ*. Yet the two forms are connected by the same mycelium. The determination of their connection with the mycelium which bears the kohlrabi heads rests on: (1) The possibility of tracing the hyphæ through the tangle which covers the garden; and (2) the production of similar swellings on the hyphæ cultivated.

In view of the difficulty of the first, and the probability that the kohlrabi heads are not diagnostic, it would seem preferable to regard the two moulds as "weeds" in the fungus garden corresponding to the *Xylaria* in the termite comb. It is not possible to determine, by tracing the hyphæ, that the termite *Xylaria* is not connected with the mycelium which bears the spheres.

It is interesting to note that Holtermann, working with termite combs in crystallising dishes, obtained only a dense growth of hyphæ which filled the dish. Apparently he wetted the combs and used vessels which were too small.

A Parallel Agaric Mycelium

So far no reason has been given why the termite sphere should be thought to be connected with the agaric rather than with the *Xylaria*. Indeed, the constant occurrence of the *Xylaria* suggests that the latter is the fungus really cultivated. But another Ceylon agaric, not connected with any insect, affords evidence which appears to justify the view taken. This agaric, *Entoloma microcarpum*, grows, not from the usual mycelium of fine hyphæ united into strands, but from a thin cake of closely packed spheres. The separate spheres are about the same size as those on the termite comb, and like the latter they appear to be composed of spherical cells. On teasing them out, it is found that the spherical cells are borne singly on the hyphæ, and form only a coating on the exterior, while the internal hyphæ swell out into oval or irregular cells, arranged either singly or in chains in the course of a hypha. In some instances these internal chains of cells show branching of the same type as that in the termite sphere. There is, however, no definite arrangement of the hyphæ—the interior of a sphere is a confused tangle of swollen cells and hyphæ. Towards the exterior some hyphæ are arranged radially, and are

continued into all the surrounding spheres. There is a fairly close resemblance between the termite sphere and the sphere of *Entoloma microcarpum*. Both show two kinds of cells, the spherical ones being confined to the exterior; and there is the same kind of branching in the oval cells of both. When the termite sphere is placed in a culture solution the parallel becomes closer: radiating hyphæ with swollen tips grow out from it, and on teasing out the sphere it is found that these proceed only from the ends of the internal chains of oval cells—the spherical cells do not produce hyphæ. The same holds good for the *Entoloma* sphere: the hyphæ which grow out to the next sphere arise from the internal chains of cells—the spherical cells do not germinate. A fringe of similar hyphæ grows from the termite sphere on the comb before it collapses, and it is conceivable that, if the requisite conditions could be realised, a mycelium similar to that of *Entoloma microcarpum* would be produced. The intervention of the ants need only be demanded to prevent this formation of adjacent spheres, and if the first spheres are eaten as soon as they are full grown, this condition is secured.

Application to Accepted Theories

But the mycelium of *Entoloma microcarpum* carries us further than this. So long as the only recognised type of agaric mycelium consisted of fine hyphæ sometimes united into strands, it was perhaps reasonable to regard the kohlrabi heads of the leaf-cutting ants as special structures evolved under cultivation by the insects. Küster regards them as galls, and Schimper states that they represent a new structure which has arisen as a result of artificial selection exercised by the ants. "These peculiar structures are a product of cultivation comparable with kohlrabi. The phylogenetic starting-point of their evolution is to be found in the tendency of the fungus to produce all kinds of swellings." It is not explained how this evolution operates, nor why the fungus should acquire a character which is being continually eradicated.

But the discovery of a normal mycelium consisting of a mass of small spheres built up of swollen cells affords another explanation. It seems most probable that Möller's kohlrabi heads are part of the *normal* mycelium of an agaric, and that their form is due to cultivation by the ants only in a small

degree, if at all. The stages of development in the nests of different species may then be attributed to differences in the agarics cultivated, and not to differences in the intelligence of the ants. The abnormalities of the fungi of the leaf-cutting ants are the simplest variations which could occur, and they can be paralleled in many other species which are not subject to the influence of insects. The spheres of the termites are far more complex, and yet they have a close parallel in the mycelium of another agaric. The conclusion is that, although the habit of cultivating fungi affords a striking instance of similarity of habit in widely separated groups of insects, it is incorrect to attribute the modifications of the hyphæ to the influence of the cultivators.

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IGNEOUS ROCK-MAGMAS AS SOLUTIONS

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Recent years have witnessed a very marked revival of interest in the rational, as distinguished from the merely descriptive, side of petrology. There is sufficient geological evidence to show that the great diversity of igneous rocks actually observed must be explained by some sort of evolution from more primitive and generalised types of rock-magmas; and the physical processes by which such "differentiation" may be brought about have accordingly been the subject of much speculation. It is clear that one prerequisite for the intelligent discussion of this important problem is a well-grounded conception of the real constitution of igneous rock-magmas with a knowledge of the laws which control their crystallisation. On the same basis must rest also our interpretation of the textures and structures of the rocks themselves, and in some measure their mineralogical composition. The question of the constitution of rock-magmas thus comes to occupy a very fundamental place with reference to petrological inquiry.

The chemical analysis of an igneous rock is commonly presented as a column of percentages of silica, alumina, and other oxides. An alternative plan, convenient for certain special purposes, is to state the composition in terms of the elements, oxygen, silicon, aluminium, etc. Again, it may be possible, either by calculation from the chemist's data or by a direct mechanical analysis, to express the composition of the rock in percentages of the several component minerals, orthoclase, quartz, biotite, etc. For a crystalline rock this last manner of representation exhibits not only the composition but the actual constitution, since it is in the form of these definite compounds that the elements are in fact combined in the solid rock. The first question to be considered is, which of the above ways of expressing the composition will likewise represent the true constitution in the case of a molten rock-magma. Do the constituents exist in the magma in combination as silicates, etc., or

as free oxides, or as elements, or in some other state of association or dissociation? The question is quite distinct from that of possible ionisation, which likewise has its importance.

Some petrologists have explicitly supposed, and others seem to assume by implication, that an igneous rock-magma is a mixture of free oxides; so that a chemical analysis in the ordinary form will represent the constitution, as well as the empirical composition, of the magma. It is not easy to imagine the apparent suspension of chemical affinities implied in such a mixture. This view involves also the supposition that the various silicate compounds known to us as rock-forming minerals are formed simultaneously with their crystallisation from the magma; which presents another difficulty, since, from analogy, we should expect such nascent compounds to appear as amorphous precipitates. The objections from the petrological side are not less weighty. If rock-magmas were merely mixtures of free oxides, and the variation which exists among rock-magmas (by whatever physical causes produced) were a variation in the relative proportions of the oxides, supposed to behave independently, we should expect a much richer list of rock-forming minerals than we have actually to record. Even from the eight most abundant oxides, which appear in all chemical analyses of igneous rocks, many minerals might be formed which do not in fact occur in this connection in nature. Some of these—such as wollastonite, monticellite, andalusite, cordierite, periclase, and others—form readily, and are frequently produced in the thermal metamorphism of sediments; but they are not found in igneous rocks, or are found only where there is reason to believe that the magma has been contaminated by absorbing sedimentary material—an exception of the kind which emphasises the rule.

Igneous rocks collectively present a very wide range of variety as regards chemical composition, and there is often great difference in this respect between parts of one and the same rock-body. Nevertheless, this diversity is brought about by the association in various proportions of minerals selected from a very limited list. Further, a given mineral occurs in very different kinds of rocks, and has therefore crystallised from magmas differing greatly in total chemical composition. It is scarcely possible to avoid the inference that the differentiation of the parent rock-magmas, to which the diversity of igneous

rocks must be ascribed, is a differentiation, not of free oxides, but of silicate and other compounds identical or closely comparable with the known rock-forming minerals themselves. We seem to be justified, therefore, in concluding that when a mineral, such as olivine, crystallises from a magma, it is not formed by the union of the oxides, magnesia and silica, in the act of crystallisation, but already existed as magnesium orthosilicate in the fluid magma. The only oxides which existed in the free state in the magma, at least near the point of crystallisation, are those parts, if any, of the silica, alumina, ferric oxide, and water which appear in the solid rock as quartz, corundum, hæmatite, and free water. For the rest, the magma is a mixture of various silicates, with a small amount of other compounds, such as phosphates and sulphides, known as constituents of igneous rocks.

It does not follow that the compounds which exist in a rock-magma at high temperatures are necessarily identical in general with those represented by the familiar rock-forming minerals. Indeed there are several considerations which induce us to qualify such conception in some important particulars. In the first place, many of the common minerals of igneous rocks belong to isomorphous series. It is not to be supposed that such a mineral as labradorite, which is an intermediate member of such a series, exists as such in a rock-magma. The two end-members of the series exist there separately, and the proportions in which they are represented in the labradorite crystals are not the same as the proportions in which they are present in the magma. A like consideration affects other well-known groups of minerals. Secondly, important examples are known, and possibly others are to be discovered, of dimorphism, and even polymorphism, among the silicates and other rock-forming minerals.[1] One form may be stable below a certain temperature and another form above that temperature. If the inversion-point falls within the range of magmatic temperatures, the transformation may take place in the magma; and it must do so, when the proper temperature is passed, if we can assume that equilibrium is always attained. Of the two principal forms of silica, quartz is, according to Allen and White, stable below 800° C., and tridymite

[1] See especially Day and Shepherd, "The Lime-Silica Series of Minerals," *Amer. Journ. Sci.*, (4) vol. xxii. (1906) pp. 265–302; Allen, Wright, and Clement, "Minerals of the Composition $MgSiO_3$; a Case of Tetramorphism," *ibid.*, pp. 385–438.

above that point. Thirdly, we may expect that chemical equilibrium will be attained in a rock-magma, as between the several compounds present, and this equilibrium will in the most general case depend upon the temperature. It is probable that in some cases reactions take place, involving important mineral rearrangements, as a consequence of falling temperature in the still fluid magma. Thus it appears that the association of orthoclase and biotite, which is stable at low temperatures, and is found so frequently in plutonic rocks, is unstable at high temperatures, and there gives place to the association of leucite and olivine, which is of common occurrence in volcanic rocks. This, which might be inferred from the nearly identical analyses of some minettes and some leucite-basalts, has been illustrated experimentally by Fouqué and Lévy. Again, Arrhenius[1] has given some reasons for supposing that, at magmatic temperatures, water is an acid capable of decomposing silicates, giving rise to acid silicates and free silicic acid on the one hand and basic hydrates and oxides on the other. Although this hypothesis rests on a rather doubtful inference from the properties of water at relatively low temperatures, it may be entertained as a possibility, which would imply a partition of acids and bases in highly heated magmas different from that which is found in the products of crystallisation.

Although these considerations may modify our conception of the nature of rock-magmas at high temperatures, they do not touch the point with which we are directly concerned, viz. that a magma in which crystallisation is imminent is a mixture of silicate and other compounds identical with those which appear when crystallisation takes place. The case of isomorphous series is no exception, since the intermediate members of such a series are not compounds, but mixtures of two (or more) compounds. Further, if every body of uniform igneous rock represents a magma which had an identical mineralogical composition, the great diversity actually found in different rock-bodies shows that the principal rock-forming minerals must be, in the fluid state, freely miscible with one another in all proportions. An igneous rock-magma is thus seen to be closely comparable with a mixture of salts in mutual solution with one another or with water.

[1] "Zur Physik des Vulkanismus," *Geol. Fören. Förh. Stockholm*, vol. xxii. (1900), pp. 395–419.

That a rock-magma is to be regarded as, in some sense, of the nature of a complex solution was suggested by Bunsen so long ago as 1861. At that time it was not possible to attach any very precise significance to the comparison of rock-magmas with ordinary solutions of salts; for the properties even of the latter were only imperfectly known, and the fundamental laws of crystallisation from saline or other solutions were yet to be discovered. The rapid advances since made in physical chemistry have placed the question on a different footing; Lagorio, Teall, Morozewicz, Vogt, and others have discussed rock-magmas from this point of view, and it is generally agreed that the only obstacles to framing a complete theory of the crystallisation of igneous rocks on the solution hypothesis are those practical ones which arise from the intractable nature of the silicate and other minerals of which these rocks are composed. The high melting-points, extreme viscosity, and other specific properties of these minerals render the direct experimental method a matter of much difficulty. Before noticing what has already been accomplished in this direction, we may point out some of the evidences from the petrographical side which seem very decidedly to assimilate the crystallisation of rock-magmas to that of those solutions which can be more easily studied.

In the first place, it has long been recognised that the freezing-points of the rock-forming minerals are not the same in magmas as they are for the minerals tested separately. This is sufficiently evident from the fact that the order in which the several minerals crystallise from a magma is not in general the inverse order of their specific fusibility. For instance, the melting-points of the alkali-felspars, and probably also of the micas and the common hornblendes and augites, lie in the neighbourhood of 1200–1250° C. For quartz experimenters have given various estimates, mostly about 1700–1800°, while, according to Allen and White, the stable form of silica at high temperatures is tridymite, melting at about 1600°. Nevertheless, quartz is usually the last mineral to crystallise in a granite. Before the conception of rock-magmas as solutions had been realised, this fact appeared anomalous; and discussion of it usually took the line of suggesting that granite is not a true igneous rock, but results from some rather vaguely defined "igneo-aqueous fusion." It cannot indeed be doubted that the presence of water is an important circumstance; but this

substance is an integral part of all igneous rock-magmas, nor is the changed fusibility of the minerals peculiar to granite or to plutonic magmas as a class.[1] The lavas poured out from Vesuvius must certainly be regarded as true igneous rocks; but everybody who has examined these has seen crystals of augite enclosed by those of leucite, though the melting-points of augite and leucite, taken separately, are about 1200° and 1420° respectively.[2] Now it is clear that the augite could not crystallise above its proper melting-point of 1200°. The leucite, which followed it, must therefore have crystallised below that temperature, that is at least 220° below its own proper melting-point. Almost any igneous rock affords similar evidence of this lowering of melting-point, or more accurately of freezing-point, of a mineral in the presence of other minerals; and we can scarcely fail to recognise in this a characteristic property of solutions.

The order of crystallisation of the constituent minerals of igneous rocks has been the subject of much discussion, as having an obvious bearing on the question of the true nature of rock-magmas and the principles governing their consolidation. Rosenbusch has laid down certain generalisations, to which, however, he admits exceptions, and indeed every petrologist knows that the exceptions are very numerous. His rules are two:—(*a*) The separation of crystals in a silicate-magma follows an order of decreasing basicity; so that at every stage the residual magma is more acid than the aggregate of the crystals already formed; (*b*) The relative amounts of the various compounds present in the magma affect the order of crystallisation, so that in general those present in less amount crystallise earlier. These two rules, if interpreted strictly, would, of course, be inconsistent with one another. The second one is the reverse of what might be inferred from the laws of solutions. It does not appear to be borne out by the facts of petrography, except in so far as concerns the minor accessory

[1] This was clearly realised by Darwin, *Geological Observations on Volcanic Islands* (1844), p. 122, foot-note.

[2] I take the figure for leucite from Brun. The determinations of Doelter and Joly are lower, though still well above those for augite. The estimation of the melting-points of the silicates is a matter of much practical difficulty; and, when the melting has been judged merely from change of shape, the temperature found must be almost always too low, the more so since natural crystals necessarily contain impurities.

minerals, which usually crystallise at an early stage, even when they are present in very small amount. It is by no means clear, however, that these minerals—apatite, spinel, zircon, and the like—are freely soluble in the ordinary silicate-minerals, as these latter are in one another. If there be only a limited miscibility, diminishing with falling temperature, the very high melting-points of these accessory minerals will ensure their early crystallisation without reference to their amount.

Rosenbusch's first rule, imposing a fixed order of crystallisation, appears at first sight equally irreconcilable with the behaviour of solutions. It is to be remarked, however, that the rocks in which such rule partially holds good, still with important exceptions, are in general rocks containing a considerable number of constituent minerals, and must therefore be compared, not with simple, but with very complex solutions. If we examine the less common rocks composed, *e.g.*, of two essential minerals, we find no fixed order of crystallisation, but one depending directly upon the relative proportions of the constituents. On Allival and the neighbouring hills, in the Isle of Rum, there is an extensive development of plutonic rocks, consisting essentially of olivine and a basic felspar, near anorthite in composition. They include every connecting link between a pure olivine-rock and a pure felspar-rock, and in a large part of them there is no other mineral except a few scattered crystals of chromite. In the varieties richer in olivine that mineral has invariably been the first to crystallise (excluding the chromite), and in varieties richer in felspar the reverse relation is invariably found. Where the two minerals are in certain definite proportions, they have crystallised simultaneously, one or the other showing its proper crystal outline in different parts of the same thin slice. The order of crystallisation in these binary rocks is thus seen to depend upon the relative proportions of the constituents, as compared with certain standard proportions.

It will be observed, however, that the behaviour here indicated is not what is seen in the crystallisation of a solution of, *e.g.*, sodium chloride and water. In the latter case only the *excess* of one or other constituent first crystallises alone, and then, when the solution has been reduced to the standard (eutectic) proportions, the two constituents crystallise together as a fine mixture of salt and ice. The apparent discrepancy

seems to be explicable by the specific properties of the bodies concerned. The silicates do not in general begin to crystallise at the proper temperatures indicated on a freezing-point diagram, but only at lower temperatures, when a considerable degree of supersaturation has been attained. Crystallisation once initiated proceeds, however, in the case of olivine or anorthite with great readiness, and large crystals may be built up very rapidly. In this way the whole of the olivine in the magma may be exhausted before the crystallisation of the felspar begins, or conversely. With minerals of less rapid crystallisation a different behaviour is indicated. Orthoclase and quartz are such a pair, and rocks composed essentially of these two minerals present a close analogy with the crystallisation of salt and water; the eutectic mixture of the two crystallised constituents being characterised very often by some special kind of intergrowth, clearly demonstrating their simultaneous crystallisation.

That the interstitial micropegmatite of acid rocks is of the nature of a eutectic aggregate was first suggested by Teall in 1888, and in his Presidential Address to the Geological Society in 1901 he returned to the subject, discussing from this point of view graphic intergrowths in general and certain types of spherulitic structures. The analogy of such intergrowths of felspar and quartz with the eutectic aggregates of Guthrie is indeed very close. Their structure is clear evidence of simultaneous crystallisation of the two minerals involved, and, as Vogt has since proved, the relative proportions of the two constituents are very closely constant, being about 74 parts of orthoclase to 26 of quartz. Further, the manner of occurrence of these intergrowths shows that they are a final residual product of crystallisation. They often make up a ground-mass, enclosing relatively large crystals either of felspar or of quartz, which we must suppose to represent the original excess of one or other constituent over eutectic proportions. With considerable probability we may extend a like interpretation to the less frequent graphic intergrowths of oligoclase with quartz or augite or hornblende, of nepheline with augite, etc. Again, we have intimate associations of a somewhat different kind between two minerals which are closely related chemically and crystallographically, though not isomorphous, *e.g.* orthoclase or microcline and albite, or augite and enstatite. Here the two

may build up composite crystals, as in the case of perthite, which is, according to Vogt's researches, a eutectic intergrowth of a potash- and a soda-felspar in the proportions of about 2 to 3.

To Professor Vogt, of Christiania, belongs the credit of the first comprehensive essay towards bringing the crystallisation of igneous rock-magmas definitely under the known laws of solutions. The starting-point of his work is a chemical, physical, and microscopical study of a large series of silicate-slags, more or less closely comparable in composition with igneous rocks.[1] A large body of information relative to these has been accumulated by Åkerman, Vogt, and others, and the use made of these data affords a striking illustration of the service which can be rendered to pure science by researches which were, in their first intention, technological.

The minerals of these slags include olivine and fayalite, monoclinic and rhombic pyroxenes, wollastonite and pseudo-wollastonite, lime-felspars, melilite, spinel, magnetite, apatite, and others. Setting aside a few which are not found as rock-forming minerals, they are the ordinary constituents of the more basic igneous rocks. The alkali-felspars, quartz, muscovite, hornblende, and some less important minerals do not occur in slags, and cannot be artificially reproduced without the aid of fluxes. The application to these minerals of the results obtained from the study of slags is therefore a matter of inference rather than of direct demonstration; but petrographical considerations, such as those concerning micrographic and perthitic intergrowths, come to reinforce powerfully the hypothesis which embraces all the rock-forming minerals under the same laws.

Vogt's principal memoir (1903-4) consists of two parts. The first part is essentially an investigation of the order of crystallisation as dependent on the relative amounts of the several constituents. Microscopical examination shows what minerals

[1] See especially *Die Silikatschmelzlösungen* (*Vidensk.-Selsk. Skrifter, Math.-Naturv. Klasse*, 1903, No. 8, and 1904, No. 1). For Vogt's earlier writings on slags see *Studier over Slagger* (*Bihang til k. Svenska Vet.-Akad. Handl.*, vol. ix. 1884); *Om. Slaggers . . .* (*Jernkontorets Annaler*, 1885); *Beiträge zur Kenntniss der Gesetze der Mineralbildung in Schmelzmassen* (*Arch. for Math. og Naturvid.*, vols. xiii., xiv., 1888–90). For a general summary of his views see *Die Theorie der Silikatschmelzlösungen* (*Bericht des V. Intern. Kongr. angew. Chemie zu Berlin*, 1903, Sekt. III. A., vol. ii. pp. 70–90). For further development of some parts of the theory, see "Physikalisch-chemische Gesetze der Krystallisationsfolge in Eruptivgesteinen," *Tscherm. Min. Petr. Mitth.*, (2) vol. xxiv. pp. 437–542, and vol. xxv. pp. 361–412 (1906).

are present, and which was the first to crystallise, while the percentages of the several constituents in the slag can be calculated from its chemical analysis. More than a hundred and fifty slags are studied in this way, and the conclusions to which the investigation leads rest therefore upon a sufficient basis. It is unmistakably established that, for slags composed of the various minerals enumerated, crystallising under atmospheric pressure without fluxes, the mineral which first begins to separate out is that which is in excess as compared with eutectic proportions. For example, the eutectic ratio for augite and olivine is about 68 to 32. From a molten slag consisting essentially of these two minerals in any other proportions than these, augite or olivine crystallises first, according as there is an excess of one or the other constituent. In like manner are determined the eutectic ratios for other pairs of constituents: plagioclase and diopside, 65 to 35; plagioclase and olivine, 70 to 30; melilite and anorthite, 65 to 35; melilite and olivine, 74 to 26; with more or less approximation in different cases.

The second part of the memoir deals with the lowering of freezing-point in mixed slags. It is shown, for example, that, while the melting-point of augite is about 1225° and of olivine about 1400°, and both minerals crystallise freely, a mixture of the two will remain fluid down to much lower temperatures. The lowest freezing-points are for mixtures in the neighbourhood of eutectic proportions, and the minimum point is about 120° below the melting-point of the augite, and 300° below that of the olivine. This lowering of freezing-point is not established by direct experiment, but from data of the total heat of fusion. Akerman determined for a large number of slags the heat required to raise a unit mass from 0° to a state of fusion. This consists of three parts, expended (*a*) in raising the crystalline slag to the melting-point, (*b*) in melting it, and (*c*) in producing a sufficient degree of superfusion to make fluidity evident. This last term is relatively small, and may be presumed approximately the same for the different slags of the series. Since augite and olivine are known to differ little as regards specific heat and latent heat of fusion, the term *b* is approximately constant for a series of augite-olivine-slags, and the term *a* depends principally upon the temperature of fusion. The measurements of total heat of fusion therefore afford an indirect means of estimating the lowering of freezing-point due

to the mutual solution of the two constituents. Similar results are obtained for olivine and melilite, augite and melilite, anorthite and melilite, etc. Thus, for several pairs of constituents, the eutectic proportions are determined by two distinct methods; first by the order of crystallisation, and secondly by the maximum lowering of freezing-point. That the results obtained by these two methods show a satisfactory agreement, to such a degree of approximation as can be expected, affords a strong inductive proof of the validity of the solution hypothesis in this application.

Taking his investigations of slags as a starting-point, Vogt has endeavoured to work out on broad lines the application of the known laws of solutions to the crystallisation of igneous rock-magmas. His presentation of the subject is to be regarded as a first sketch, to be corrected and completed in the light of further knowledge. At present serious limitations are imposed by our ignorance of the thermal and other physical properties of the silicate and other compounds which take part in the composition of the rocks, and experimental research in this direction is the first requisite before the petrological inquiry can be prosecuted farther. That the difficulties of such research, though great, are not insuperable is proved by the work already accomplished in the Geophysical Laboratory of the Carnegie Institution at Washington.[1]

Meanwhile it appears that the data furnished from the petrographical side are quite sufficient for testing some of the more important principles, and for obtaining specific results which have at least an approximate value. The interpretation of the porphyritic structure will illustrate this. The porphyritic crystals in lavas may often represent, as supposed by Rosenbusch, the result of "intratelluric" crystallisation, prior to the extrusion of the magma; in which case these elements and the general ground-mass belong to two distinct stages of crystallisation, divided by an abrupt change of physical conditions. Several petrologists, however, have pointed out that there are grave difficulties in framing an explanation on these lines for the porphyritic structure in intrusive rocks. Into the arguments

[1] Day and Allen, *The Isomorphism and Thermal Properties of the Felspars* (1905); also in *Amer. Journ. Sci.*, (4) vol. xix. (1905), pp. 93-142; Allen and White "On Wollastonite and Pseudo-Wollastonite," *Amer. Journ. Sci.*, (4) vol. xxi. (1906), pp. 39-108; with other papers already cited.

advanced on this question by Zirkel, Cross, Pirsson, and others it is not necessary to enter. The laws of crystallisation of solutions lead at once to a general interpretation of the structure, which is independent of any discontinuous change of conditions. The porphyritic elements are to be regarded as representing approximately the excess of particular constituents over the eutectic proportions, and the ground-mass the eutectic mixture itself. This view, clearly set forth by Becker, has been discussed by Vogt for the particular case of the felspar-quartz-rocks. The data are provided by a large series of comparative analyses (of total rock, porphyritic crystals, and ground-mass) published twenty years ago by Lagorio. Many of these represent rocks composed essentially of felspars and quartz, with only a small proportion of ferro-magnesian minerals. They differ rather widely in bulk-analysis; and still greater difference is seen in the porphyritic elements, which are sometimes felspars, sometimes quartz, sometimes both felspars and quartz. The analyses of ground-mass or glassy base show a notably smaller range of difference. For rocks with about 74 per cent. of silica the ground-mass has approximately the same composition as the whole; for more acid examples the ground-mass is less acid than the whole rock, owing to abstraction of quartz in the form of porphyritic crystals; for more basic examples the ground-mass is more acid than the rock, owing to the abstraction of felspar. There is thus in the ground-mass of such rocks a tendency towards a certain standard composition, with about 74 per cent. of silica, agreeing so far with the eutectic mixture of felspar and quartz as determined from graphic intergrowths.

It is important to remark, however, that, while this tendency is unmistakably indicated, the ideal eutectic composition is in most cases realised only with a rude approximation. Analytical errors and the disturbing influence of the ferro-magnesian constituents present will account for some part of the discrepancy, but there are more important reasons. The rocks analysed by Lagorio are almost all volcanic rocks, in which therefore the progress of crystallisation has generally been interrupted by an abrupt change of conditions; and this break may often have occurred before the excess of one or other constituent had completely crystallised out. Especially, we have to reckon with the consequences of supersaturation in the magma. Vogt has shown that this consideration not only goes far to account for the

variable composition of the ground-mass, but also throws light upon features which would otherwise be anomalous; notably the occurrence of both felspar and quartz among the porphyritic elements in the same rock, and the evidence sometimes seen of early crystals having been partly redissolved by the magma.

A mineral does not necessarily begin to crystallise from a magma at the theoretical freezing-point. This freezing-point (for a definite compound the same as the melting-point in the same magma) is the temperature at which crystals of the mineral are in equilibrium with the magma. But equilibrium is not established in the absence of crystals, and the temperature may fall considerably below the freezing-point before any crystallisation is set up. If we may apply to rock-magmas the results of Professor Miers' researches on saline solutions, crystallisation can in no circumstances be initiated, without "inoculation" by solid crystals of the same substance or one isomorphous with it, until a certain definite degree of supersaturation has been attained; and there are many indications that for the rock-forming minerals the requisite supersaturation is very considerable. Crystallisation once started, the latent heat evolved soon raises the temperature to a point at which equilibrium is adjusted.

Suppose, now, a magma consisting of quartz and felspar, with an excess of the former above eutectic proportions. Cooling having brought about a sufficient degree of supersaturation, quartz begins to crystallise, equilibrium is attained with some rise of temperature, and the separation of quartz proceeds with falling temperature. When all the excess of quartz is separated out, and the magma thus reduced to eutectic composition, felspar should begin to crystallise simultaneously with the quartz; but, since no felspar-crystals are present to establish equilibrium, this will not yet take place. The quartz-crystals will continue to grow alone, until the magma is sufficiently supersaturated with felspar to start the crystallisation of that constituent. The rapid crystallisation of the felspar will set free enough heat to raise the temperature and also to redissolve part of the quartz, with which mineral the magma is now undersaturated. When the eutectic point is again reached, the presence of crystals of both minerals will prevent any further supersaturation. In this illustrative case it is easy to see that the intervention of supersaturation causes consider-

able modifications in the petrographical character of the resulting rock. In the first place the porphyritic elements include felspar as well as quartz. Secondly, the total amount of the porphyritic crystals is greater than it would otherwise be, and the amount of ground-mass is correspondingly reduced. Thirdly, the quartz crystals are corroded, as a normal incident of the progress of consolidation and without any discontinuity of external conditions.

An important question relative to the solution theory of rock-magmas is that of the ionisation or electrolytic dissociation of the several constituents of the magma. In an aqueous solution of salts the water plays a special part, inasmuch as it serves as a medium in which the other constituents become more or less dissociated into ions, while the water itself is little, if at all, affected. We cannot point to any constituent of an igneous rock-magma as playing this passive rôle, but it cannot be doubted that there is in such a magma a notable degree of dissociation of some or all of the constituents. This follows from the fact, established by Barus and Iddings, that rock-magmas are conductors of electricity. They showed further that the conductivity is increased by rise of temperature, and that, of the different magmas tested, the most acid one is the best conductor. Beyond this we have no direct knowledge of this subject. From analogy we may probably infer that, for a given electrolyte at a given temperature, dissociation is more advanced in proportion as the amount of this constituent in the magma is less. The particular ions into which a given electrolyte breaks up may be set down with some confidence for the simpler rock-forming compounds. We may assume, for instance, that the positive ion of enstatite is magnesium, that of orthoclase potassium, etc.

Electrolytic dissociation is one factor in determining the mutual lowering of freezing-point and the eutectic ratio between two bodies in mutual solution. In a solution containing three or more constituents the interaction depending on dissociation is of a more complex kind, and it may result that the eutectic ratio between two constituents is very notably altered by the presence of a third. In particular, the solubility of any constituent is diminished by the presence of another which has one ion in common with it. Now most rock-magmas contain a considerable number of minerals, and it frequently happens

that two or more of them have an ion in common, such as potassium or magnesium, or the electro-negative group SiO_4 (in orthosilicates) or SiO_3 (in metasilicates). It is therefore probable that the law of the common ion, first deduced by Nernst, is an important one in application to rock-magmas. Vogt invokes it more especially for the case of the minor accessory minerals, which almost always crystallise very early, even when they are present in very small amount. Some of these minerals (spinel, chromite, zircon, etc.) have very high melting-points, and it is probable that the eutectic mixture of, say, spinel and a felspar contains a small proportion of spinel to a large amount of felspar. This, however, would not be sufficient to account for the constantly early separation of spinel. But almost any natural magma will contain in addition one or more constituents (olivine, pyroxenes, biotite) which have one ion (magnesium) in common with the spinel; and the presence of these may displace the eutectic point so far away from spinel as to cause that mineral to crystallise first, even when the proportion of it in the mixed magma is very small. Similarly apatite, perofskite, and sphene have one ion (calcium) in common with lime-felspar; zircon has the group SiO_4 in common with any orthosilicate compound; and so for other cases. Nor is it only in respect of these minor accessory constituents that Nernst's law may be supposed to have importance. It may afford an explanation of the strong tendency of olivine to crystallise at an early stage from magmas which contain pyroxenes. It has already been remarked, as an illustration of the simple eutectic law, that in the olivine-felspar rocks of Rum one or other mineral has crystallised first, according to the relative amounts of the two. Associated with these rocks are others containing augite and enstatite in addition to the above constituents, and here it is seen that the olivine has crystallised first, even when the felspar was largely in excess.

Where positive knowledge is so scanty, dogmatism would be out of place; but there seems to be good reason for believing that this interaction dependent on ionisation is actually operative in rock-magmas, and accounts for facts which would otherwise appear anomalous. It tends to make the order of crystallisation depend less upon the relative proportions of the several constituents and more upon their specific properties. In other

words, it is a factor which makes for a certain standard sequence of crystallisation of the several rock-forming minerals, and it serves in part to account for such measure of truth as can be claimed for the empirical laws laid down by Rosenbusch.

Limitations of space preclude any discussion of other branches of our subject, and in particular of the application to rock-magmas of Bakhuis Roozeboom's investigations on isomorphous mixed crystals. Enough has perhaps been said to show the interest which attaches to this view of the process of crystallisation in igneous magmas, and the promise which it offers of further development. When a sufficient body of quantitative data has been accumulated by research in the laboratory, the solution theory of rock-magmas will become the proper physical basis of all investigation and speculation in the domain of petrogenesis.

THE ORIGIN OF THE "FLOWER"

By W. C. WORSDELL, F.L.S.

A TYPICAL flower, such as a buttercup, consists of a central conical disc or receptacle on and around which are seated four distinct sets or groups of floral organs; the outermost set of five green leaves is the calyx, the second whorl of brilliant yellow leaves is the corolla; then follow in succession a large number of *scattered* stamens, or a few arranged in a whorl, and finally a (usually) corresponding number of carpels (the seed-bearing organs).

If we carefully dissect a flower, and examine all its parts, it becomes clear that in a flower we are concerned not with something entirely new and distinct from every other part of the plant, but merely with a modification of an ordinary leafy shoot; for the central disc is a highly contracted and shortened shoot; the sepals, petals, stamens, and carpels are all leaves which have been in various degrees modified and altered to suit the specific functions which they have to perform in the economy of the plant's life. It was Caspar Friedrich Wolff[1] who was the first to hint at the origin of the flower as being the outcome of a gradual metamorphosis of the foliage-leaves situated at a lower level on the plant. He held that the production of floral leaves was the result of a degeneration in the quality of the sap, the richer portion being used up at a lower level by the first-formed vigorous foliage-leaves. Goethe,[2] however, first established the theory of the underlying homology of all foliar organs of the plant. His main idea was that the floral leaves represented the final stage in a gradual ascending metamorphosis of which the foliage-leaves are the starting point, and that the production of flowers is due to an improvement and etherealisation of the sap during its ascent through the plant. All foliar organs, he said, are variants on an *ideal*

[1] *Theoria generationis*, 1759.

[2] *Versuch die Metamorphose der Pflanzen zu erklären*, Gotha, 1790 (*Essay on the Metamorphosis of Plants*, translated by Emily M. Cox in Seemann's *Journal of Botany*, vol. i. 1863).

type-leaf. The well-known German botanist Goebel[1] regards the *foliage*-leaf as the type of which all other kinds of leaf are modifications. The fact that a "flower" is, after all, only a highly modified leafy shoot is shown by the frequent occurrence in our gardens and in Nature of those peculiar "sports" known as "floral proliferations," in which the usually shortened axis of the flower elongates, under the influence of certain factors, as, *e.g.*, excess of nourishment in the soil, into a leafy shoot, while the floral leaves become, in part or wholly, changed in texture, colour, and size, so as to resemble ordinary foliage-leaves, frequently producing at the same time branches in their axils. Roses not rarely exhibit this "freak."

The above considerations enable us to see of what other parts of the plant the flower is the natural equivalent. The central conical disc or receptacle is after all merely a highly contracted or shortened shoot on and around which the various foliar organs of the flower are seated. It is probable that, as Goebel believes, each type of floral leaf, whether sepal, petal, stamen, or carpel, has been derived by modification of form and function, and reduction in size, of green foliage-leaves. We shall see more clearly how this came about further on.

In the meantime we may note that it is almost certain that the flowers of the most primitive Angiosperms did not possess a double perianth (calyx and corolla) such as we see to-day in the Lily and Buttercup. Many of our present wind-fertilised flowers, such as the Poplar, Oak, etc., have either no perianth at all or a *single*, colourless, ill-formed one. How far this condition is a case of reduction from much better-furnished types we hardly are able to estimate. The consensus of opinion to-day seems to point to the fact that the *petals*, at any rate, are a comparatively recent formation within the flower. It was Grant Allen[2] who first pointed out that petals are in all cases derived by modification of pre-existing stamens. Nägeli[3] and then Drude[4] also maintained this position. Celakovsky,[5] in

[1] "Die vergleichende Entwickelungsgeschichte der Pflanzenorgane" (Schenk's *Handbuch der Botanik*, vol. iii. part i. p. 100, 1884).

[2] *The Colours of Flowers*, 1882.

[3] *Mechanisch-physiologische Theorie der Abstammungslehre*, p. 496, 1884.

[4] "Die systematische und geographische Anordnung der Phanerogamen" (Schenk's *Handbuch*, vol. iii. part ii. 1887).

[5] "Ueber den phylogenetischen Entwickelungsgang der Blüthe," etc., part i. p. 7 (*Kgl. böhm. Gesellsch. d. Wissensch.*, Prag, 1900).

an interesting comparative study of the Ranunculaceæ, showed that in all probability both petals and sepals are derived from stamens. On the other hand, Prantl[1] held that the corolla, along with the calyx, arose from the metamorphosis of bracts or bracteoles situated below the flower. Goebel,[2] while admitting that in the majority of cases petals have arisen from stamens, inclines to the belief that in other cases petals, as well as sepals, have taken origin from bracts. In a paper[3] published four years ago I supported Celakovsky's view on the matter, viz. that both sepals and petals are in *all* cases derived from stamens.

The phenomena presented by many double flowers, *e.g.* the garden rose and daffodil, clearly disclose the staminal origin of the petals, for all transitions may be found between a sharply defined and typical stamen and an ordinary petal, and the stamens undoubtedly existed prior to this latter.

So far, then, investigation by means of the study of the comparative morphology and teratology (especially the latter) of organs has revealed to us that the "flower" is the *homologue* or *morphological equivalent* of a vegetative leafy shoot, of which the foliar organs, along with the axis on which they are borne, have been peculiarly modified for the purpose of subserving the special functions characteristic of the "flower." Inasmuch as the great majority of "sports" or teratological phenomena represent *reversions*, or attempts at reversions, to a primitive condition of the organs concerned, we may, perhaps, infer that the flower which has proliferated into a leafy shoot is at the same time yielding us a clue to the ancestral condition of that structure. Yet this is by no means *necessarily* the case; and I think it would be quite unwise at this stage of our knowledge to draw such a conclusion from such a teratological structure. For if a "flower" and a leafy shoot are *homologous* structures, this can only mean, in the long run, that both have been derived from a common ancestor; and this being the case, it is surely possible and, I would add, probable, that each of these structures contains within it *the potentialities of the other*, and, given the appropriate environmental stimulus, is capable of exhibiting its characteristics.

[1] "Beiträge zur Morphologie und Systematik der Ranunculaceæ" (Engler's *Bot. Jahrbücher*, vol. ix. 1887).

[2] *Organographie der Pflanzen*, vol. ii. 1901.

[3] "The Origin of the Perianth of Flowers" (*New Phytologist*, vol. ii. no. 2, 1903).

Let us now turn to the *phylogenetic* aspect of this subject. For this purpose I must refer to the habit and morphological structure of certain plants occurring chiefly in the Palæozoic formation of the coal measures. These are the "Seed-ferns," of which we now know several forms. The stems known as *Lyginodendron*, *Heterangium*, and *Medullosa* bore large Fern-like fronds of usually very complex organisation. Some of these leaves were purely vegetative, others bore the reproductive organs, and with, as a rule, their green laminæ greatly reduced or quite absent. In some cases, however, the fertile leaves or sporophylls appear to have had their laminæ but little, if at all, reduced. The fossil known as *Crossotheca* is the fertile portion of the foliage of *Lyginodendron*; it is that part of the foliar organ bearing the male sporangia, and these are situated on the lower surface of round, flat subdivisions of the much-divided leaf. *Lyginodendron* stems are also known to have borne reduced[1] fertile fronds which produced large seeds, or, more strictly speaking, bodies intermediate[2] between sporangia and seeds, known as *Lagenostoma*, at the *end* of short subdivisions of the frond-pinnæ.

Neuropteris, the foliage of some of the stems known as *Medullosa*, also bore similar large seed-like bodies. *Pecopteris Pluckeneti* is a scarcely modified vegetative frond bearing hundreds of seed-like structures along the margins of the pinnæ. All these plants were probably derived from true Ferns or Fern-like plants bearing on their leaves a single kind of sporangium only, as in *Marattia*. The few facts already stated are sufficient to show that at this period of the world's history there was a group of plants bearing large, complex Fern-like sporophylls of two kinds, some producing male sporangia, others seed-like organs. Whether the same individual plant bore both kinds of sporophyll, and, if so, how they were respectively situated with regard to each other, is not at present known. It is quite likely that the plants were diœcious, the male and female organs occurring on separate plants.

[1] *i.e.* as regards the production of green laminæ.

[2] These bodies are not really seeds, as that term is understood when applied to the corresponding organs in flowering-plants, for the reason that they *do not contain embryos*, the effects of fertilisation, if not that process itself, only being reached after the organ had fallen to the ground.

Passing on, now, to the next great geological epoch, viz. the Mesozoic, we find abundant remains of plants both in Europe and, more especially numerous, in the United States of America, which are known as the Cycadeoideæ or Cycad-like plants, or sometimes as the Bennettiteæ. Just as the "Seed-ferns" may be regarded as forms intermediate in character between the true Ferns and Gymnosperms generally, so these Cycadeoideæ may be regarded as being intermediate between the "Seed-ferns" and our modern living Cycads. The structure, both external and internal, of their stems and of their leaves, as well as their general habit, is almost identical with that of the Cycads. But in the character of the reproductive organs they diverge widely from those plants. Unlike the "Seed-ferns," the sporophylls of the Cycadeoideæ differ altogether from the vegetative or foliage leaves of this group; these latter resembled those of modern Cycads, consisting each of an elongated rachis bearing on each side a row of simple undivided pinnæ, being thus much simpler in organisation than the foliage-leaves of the "Seed-ferns." Now, while it is true that the sporophylls of some members of the latter group were considerably reduced as regards the laminar development of their fronds, yet they still exhibited the same general complexity of subdivision into minute segments as the foliage-leaves, and it is not unlikely that the two kinds of foliar organ were mixed together on the plant, or, at any rate, were borne on the same main axis. But in the Cycadeoideæ the sporophylls are restricted to special, very short branches occurring in the axils of certain of the leaves of the main stem. Dr. G. R. Wieland, of Yale University, Connecticut, has described[1] for us numbers of these plants, which he has obtained chiefly from the Black Hills of Dakota. The peduncle of the short fertile branch or cone is clothed with simple bracts, which enclose it entirely in the bud-condition. At the upper end of the peduncle, where the bracts cease, is borne a whorl of male sporophylls, which are connate below to form a kind of cup or enclosing wall. The complexity of organisation of these male organs reminds one again of those of the Seed-ferns, and indeed they are very Fern-like, although it is evident that very considerable reduction in complexity has taken place during their descent from the sporophylls of the Seed-ferns. For

[1] *American Fossil Cycads*, 1906.

these male organs of Cycadeoideæ are merely pinnate, as regards the purely vegetative portion of their fronds, thus resembling the foliage-leaves of this group. Each pinna bears along its axis two rows of compound sporangia or synangia, this character giving them a decided resemblance to the Marattiaceous Ferns. These fronds are, thus, if we take their synangial subdivisions also into account, bipinnate. The main rachis has a sterile terminal expansion. They have a circinate vernation; on the whole, therefore, a very Fern-like or Seed-fern-like organisation. They ripen before the female sporophylls, and are completely shed before the latter mature. With the consideration of the male sporophylls we drop the last link of relationship and resemblance of these plants with the Seed-ferns. For in the female sporophylls we have revealed to us structures of a totally different and quite new character. They are borne in great numbers either all over a rounded and fairly flat cushion, representing the much-shortened axis of the cone, or else, in other types, along the lateral surface of an elongated conical axis, from which they project at right angles. Each sporophyll is a long, very slender stalk, of radial symmetry of structure, bearing at its top a female sporangium or seed; this latter contains an embryo and either a very small amount of endosperm, or none at all. Equally numerous with the seed-bearing sporophylls, and scattered amongst them, are organs which we may assume to be of the nature of sterile sporophylls, which have become modified to subserve the function of a protective pseudo-pericarp; for each of them is expanded at the top in such a way as to overtop and enclose the seeds of the neighbouring fertile organs, leaving only a narrow orifice for the projection of the micropylar beak.

Certainly the most plausible view of these seed-bearing pedicels is that they are sporophylls; but if so, how greatly modified, how enormously reduced from the large, complexedly organised female sporophyll of the Seed-ferns! Yet this need not surprise us. For it is just this process of *reduction* in complexity and in size which we discover to be a constant concomitant of evolution in whatever direction we turn our gaze. The passage, in fact, from the reproductive department, so to speak, of the organisation of the Seed-ferns to that of the Cycadeoideæ has been effected as follows: The sporophylls have been reduced in size and complexity of structure at the same time that they

have been segregated from the foliage-leaves, not only in the sense that the reproductive bodies came to be borne on special foliar organs set apart for that purpose, but also in the sense that these latter were relegated to special branches of the plant which both in appearance and in all the characters of their constitution were as distinct as may be from any of the other branches or from the main stem of the plant.

The above are, in fact, none other than the radical changes in organisation which have brought about the appearance in the world of plants of *some* of those characters the *ensemble* of which produce what we call a "flower." In the reproductive branch of the Cycadeoideæ I believe we see a picture or representation of the primitive or ancestral "flower." There, in the first place, is the perianth in the shape of the bracts, situated on the peduncle and subtending the whole. The male sporophylls are connate below and cyclically grouped, just as is the case with the stamens of so many true "flowers"; but they are still of highly complex organisation, and are very far from showing any resemblance to a "stamen." Still more is this the case with the female sporophylls, which are so exceedingly modified as to bear not the remotest resemblance either to the corresponding organ in the Seed-ferns or to the "carpel" of a "flower." However, they somewhat resemble a "stamen" of the higher plants in general organisation, and must have been derived from a Fern-like sporophyll, just as I believe a stamen has been derived from such.

These seed-bearing organs of Cycadeoideæ are arranged spirally on an elongated receptacle, strongly reminding one of the precisely similar arrangement in such a "flower" as that of the Magnoliaceæ. The hermaphrodite constitution and the relative mutual positions of the two kinds of sporophyll are also exactly those obtaining in a typical "flower" of the Angiosperms.

These Bennettitean "flowers" were probably wind-fertilised; yet in view of the *proterandrous* character of the structure, it is not an impossible conjecture that there existed a process of fertilisation by means of insects, though we do not know what attractions there may have been which would induce their visits. Yet it is an interesting fact that, as I have heard it stated on authority, the first Lepidopterous insect is believed to occur in the Stonesfield Slate, a formation which represents the period when these Cycadeoideæ flourished.

Therefore it is not unlikely that in this peculiar structure we see the first real "flower," though devoid as yet of anything of the nature of a coloured perianth. It must not be supposed, however, that our "flowering plants" have been derived necessarily from Cycadeoideæ producing "flowers" such as I have just described. It is quite likely that the Angiosperms sprang from a stock lower down, nearer the Seed-fern stem, and developed along lines parallel and analogous to those of the Cycadeoideæ, forming reproductive structures more truly approaching and resembling the Angiospermous "flower" than do those of the Cycadeoideæ, which are, it must be admitted (a glance at the male and female sporophylls is enough to show this) still very remote from the "flower" of the higher plants.

In any case, enough has been said to show (with a large probability of truth) how, returning to the point from which we set out, a "flower" is the result of the extreme modification of a leafy branch or of a portion of the main axis, the axial part of which has been excessively shortened and contracted, and the perianth-leaves, stamens, and carpels reduced and altered from the condition of large, Fern-like foliage-leaves. Thus, in the long run, it is the Ferns that we have to thank for our Flowers.

ECONOMIC ORNITHOLOGY IN RELATION TO AGRICULTURE, HORTICULTURE, AND FORESTRY

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The subject of the economic status of wild birds is one that has to be approached in so many different ways that it is almost impossible to formulate any satisfactory plan of treating this important matter.

In the conclusion of any remarks on this wide subject one is always led away into one's own opinion. Even after having weighed the evidence for and against the utility or otherwise of birds, the final summing-up is so frequently at variance with that of others—others probably better competent to judge —that one doubts whether this vexed question had not better be left alone as a never-to-be-solved problem.

There are people who have a sentimental love for birds, and say none should be destroyed; there are others who have lost, and continue to do so, many pounds, shillings and pence owing to the harm done by birds, and they say destroy them all; a few more cautious people say keep down any excess of so-and-so, but encourage and protect the rest. It is a question of sentimentalism, or of the stern reality of life—pounds, shillings and pence.

Any one hearing the sweet call of the Thrush and Blackbird in spring must experience a sensation of joy, and forget their prospective loss of strawberries and apples. The death-like silence of the Norwegian forests would be unbearable but for the plaintive note of the Redwing, which has gained for it the name of the Norwegian Nightingale; the desolation of the snow-covered, frost-bound Canadian prairies is surely made bearable by the occasional "Whiskey Jack" pecking at the frozen meat outside the tent.

There are other things, it is true, than the mere economy of

bird-life. Did not the ancients name that unwholesome lake Avernus the Mouth of Hell, because it was birdless?

It is frequently put forward by those who strive to protect bird-life that birds act as natural checks to the undue increase of insect and molluscan life. This may be so. But in connection with this we must bear in mind that in those countries in which small birds are shot at all times of the year, insect and other pests are no worse than where birds are protected by law. In some cases at least, where birds are always killed and are scarce, as in parts of France, Italy, and Belgium, insect and other pests are not so harmful, weeds are no more abundant in the fields than with us in Britain.

It is much easier, we all know, to keep down weeds by proper and cleanly cultivation than it is to stop birds damaging our crops, fruit, seed, and trees. We must also bear in mind that birds distribute seeds.

When the earth was peopled by animals and birds alone, when even man was scantily present, when Nature, not man, ruled the world, then birds played their part in keeping the balance of nature and in spreading vegetation.

The Rooks undoubtedly account for the natural distribution of oaks, carrying the acorns from place to place and dropping them *en route*. Man sets his own plantations now; what does it matter what the Rook does? many will say. On the other hand, there are many things that birds do for man which he himself could not do except at very great expense.

What would be the state of our permanent pastures if there were no birds? In a few years thousands of acres would probably be bared by subterranean insects. Were it not for Rooks, Jackdaws, Starlings, Plovers, and Gulls, the white-grubs, wireworms, leather-jackets, etc., would increase in such enormous numbers that the grass would be destroyed wholesale. Has any man devised, or is any man likely to devise, a plan of so treating pasture land as to kill all those persistent and ever-increasing enemies? Until he does so we must rely on nature.

Even the sowing of seeds by birds is of some benefit, for the Nutcracker prefers high mountain regions, where planting is very costly, and the assistance to man in this respect is of great value.

Such birds as have been mentioned above, of course, do some harm elsewhere by destroying seed-wheat, maize, fruit, and forest seeds.

We must look at these matters from the point of view of a debtor and creditor account.

Every one acknowledges that birds to get their food eat and destroy *things* of various sorts. The *things* birds obtain for food may be classed under three headings for economic consideration : namely, (i) matter of use to man for food for himself and his domesticated animals, such as seeds, fruit, roots, and stock, and also those beneficial animals which act as natural checks to those which are injurious ; (ii) other living creatures that are directly harmful to us, such as injurious insects, ticks, and mammals, weeds and weed seeds, and indirectly sickly game birds, which can only breed degenerated stock ; (iii) carrion and refuse, shore garbage, etc., as we find is done by Crows, Gulls, Storks, and Vultures.

Our game-birds form a separate group. Some of the latter, such as Pheasants, do some harm to the farmer, the Capercaillie to the forester ; but they also do much good, besides being valuable for food and sport.

Unfortunately we must acknowledge that the first section is very important. Birds destroy our fruit, seeds, and crops, damage our forest trees, attack our game-birds and poultry, and even young stock ; they wantonly destroy young buds of trees and bushes ; they destroy beneficial insects and distribute injurious ones ; they disseminate weeds, and they are harmful to our fisheries. But one must bear in mind the good they do by destroying injurious insects, other birds and mammals.

We must consider them individually from a debtor and creditor point of view. If we do so with an open mind we shall find a few on one side of the ledger, a few on the other ; but the majority in which the account is nearly equally balanced. If we look carefully into the last-named we shall find the subject becomes a very complex one, and we are bound to confess that we do not at present know sufficient about them to say whether or not they are worth keeping on the books.

As far as we go in Britain, there is only one way in which we at present are likely to arrive at any definite general conclusion on this subject that can range outside that fatal error in such cases, namely, "personal opinion." That is, by the appointment of a departmental committee to collect all evidence from all parts of the kingdom from farmers, gardeners, fruit-growers, foresters, gamekeepers, and field ornithologists. Until

this is done, and done thoroughly, we shall still be struggling with the personal opinions of people who look through glasses with very different eyes. The serious question is, do the people who are mentioned as witnesses know enough yet to express a definite opinion? Have we sufficient evidence as to the actual food of birds at different times of the year and under varied conditions? We feel bound to answer in the negative. What we want is more of such work on their food as has been recorded by Mr. J. Gilmour (16).

The present paper deals with birds from the economic point of view mentioned above without expressing any personal opinions whatsoever.

Roughly speaking, we have two hundred and fifty birds which we may call regular residents of, or constant migrants to, these islands. A large number of these are rare or uncommon, and are wisely protected by law, or should be. No more than sixty can be said to be of any real economic importance. A number of these are almost exclusively beneficial, such as the Swallow, Martin, Swift, some Warblers and Waders, etc. These we may discard for present purposes. Some of the remainder are of general interest, such as the Hawks and Owls. Others are mainly connected with the forest, such as the Woodpeckers; yet others affect for good or evil the fruit-grower, as the Bullfinch, Blackbird, and Tits; the farmer has such as the Rook, Starling, Sparrow, and Plover constantly before him; and the gardener the Finches generally.

An interesting subject has recently become prominent, namely, the change of habits in birds (1, p. 74), but it does not seem that anything like sufficient evidence has been collected to give any scientific status to this subject. Isolated cases quoted could be reduplicated a hundredfold, and thus the apparent sudden change in one district loses much of its significance.

The so-called "Birds of Prey"—the Hawks, Falcons, and Owls—have always been subject to persecution at the hands of gamekeepers; fortunately a certain amount of discrimination now takes place in the shooting and trapping of these Raptores. Their food in this country consists mainly of small mammals and birds. Any great excess of mice, voles, etc., is always followed by an influx of these rapacious birds. It seems, however, that they come when these creatures are in such excess

that already enormous damage has been done. Man has already had to take, or tried to take, steps to check these increasing animals. When also a certain stage of excess has been reached, disease breaks out and the rodents die off in thousands. Nevertheless, we must bear in mind that mice, rats, and voles form a very large part of the bill of fare of such birds, and thus they must to some extent keep their undue multiplication in abeyance. In connection with the plague of voles and mice in South Scotland in 1892, we learn that "a preponderance of opinion amongst farmers is reported tracing the cause of the present outbreak to the scarcity of owls, kestrels, hawks, weasels, and other vermin" (17, p. 4).

Moreover Hawks, Falcons, and Harriers undoubtedly take sickly game (although some say this is not so). This must in the end prove beneficial, for their progeny are more likely to prove unhealthy than that of strong stock.

The Kestrel (*Falco tinnunculus*, Linn.) is certainly beneficial in its habits, for it feeds almost entirely on mice, voles, young rats, small birds, beetles, and grasshoppers. It is generally acknowledged to be helpful to man, save by gamekeepers, yet it rarely touches either game or poultry; but according to the Rev. Henry Slater (2) "a rogue kestrel, with a hungry young family of its own to provide for, learns bad habits, and visits the pheasant coops." This is certainly from the general evidence at hand very exceptional, and all, save the majority of gamekeepers, who can discriminate between our Hawks, acknowledge its beneficial nature. With the Sparrow Hawk (*Accipiter nisus*, Linn.) there seems to be a great difference of opinion. Mr. Fred Smith (3) says it "is too fond of game and poultry to be protected"; on the other hand, the Rev. Henry Slater (2) says it is "certainly not injurious from a farmer's point of view . . . its influence on the farm must be called mildly beneficial." The consensus of opinion is undoubtedly against the Sparrow Hawk. Every one interested in poultry or game is well acquainted with its destructive habits.

The Peregrine (*Falco peregrinus*, Tunstall) may be classed with the Sparrow Hawk as being harmful to game and poultry, but we must bear in mind that it devours rats, mice, and voles. The question is, does the amount of good these two birds do compensate us for the amount of harm? It is very doubtful if this question is ever likely to be satisfactorily answered.

We have to consider the harmful creatures they devour. Can we destroy them easily? If so, then the good they do must be discounted. In the case of voles and mice we must acknowledge we cannot, and thus it seems the good done must far outweigh the evil.

There is no dispute about Owls. The Barn Owl (*Strix flammea*, Linn.), the Short-eared Owl (*Asio accipitrinus*, Pallas) live mostly on voles, long-tailed field mice, and small birds; the Tawny Owl (*Syrnium aluco*, Linn.) is a great devourer of finches. The Long-eared Owl (*Asio otus*, Linn.) alone has anything against it, as it is now and then troublesome to the gamekeeper.

With the family Corvidæ we come to a group subject to any amount of discussion and divergence of opinion. Those that are of economic importance are the Rook, Carrion Crow, Hooded Crow, Jackdaw, Jay, and Magpie.

The Rook is one of those birds about which we hear incessant discussion. Many farmers seem inclined to favour it. The Rev. H. Slater (2, p. 248) says: "This bird is rather a problem at present. I have no hesitation in expressing my belief that it is a most useful friend to agriculture on the whole, *if not allowed to increase in numbers abnormally*" (the italics are mine). Mr. Cecil Hooper (1, p. 80) mentions the damage they do to fruit, eating green strawberries, cherries, gooseberries, sometimes apples and pears, walnuts, cobs and filberts, and records a case of their damage to raspberries at Blairgowrie, in Scotland. He then says: "In order to keep the number of rooks under control, the newly-fledged birds in a rookery should be shot, say two out of each nest, in order to make the number stationary and not increasing."

In connection with the Rook, Mr. J. Gilmour's report (16) must be quoted. He says as follows: "While I was prepared to find that facts were all against the Woodpigeon, I was, I confess, in hopes that our particular inquiries into the diet of the Rook would clearly prove that, if not over-abundant, he might to a considerable extent be a friend to the farmer. Judging from the results of this special investigation, as tabulated, I fear figures go badly against him."

There is no doubt whatever that Rooks take a great deal of seed-corn and even potatoes in dry weather. Attacking stacked corn (16) is surely unusual. But, on the other hand,

for the greater part of the year they feed almost exclusively on wireworms, leather-jackets, chafer larvæ, fever fly (*Bibio* spp.) larvæ, and other grubs in the soil, and also various caterpillars, such as winter moth and even the lackey moth, which has so few natural enemies.

It may be said that by banding the trees we can keep the winter moth in check, and by spraying, the lackey moth; but one must remember that both occur in our woods and forests, the former often in enormous numbers, and from thence spread to fruit plantations near at hand. Moreover, the Rooks feed on that destructive Green Tortrix (*Tortrix viridana*) which too frequently defoliates our oak-trees.

That the Rooks do an enormous amount of good there is no doubt; at the same time every one acknowledges that they do some harm. The farmer has to scare them off his seed-corn and even young roots; the fruit-grower rarely off his fruit. Its attack on stacked corn in Fifeshire (16) seems to be local. The cost of scaring off five thousand rooks is no more than for fifty. Yet five thousand rooks will do an appreciable amount of good; fifty will do one hundred times less good. Where, therefore, is the logic of recommending their reduction in numbers?

The Common Crow (*Corvus corone*) is not of any great importance, but now and then is destructive to game eggs and even sickly lambs. The Hooded Crow (*C. cornix*) is said to be "not abundant enough to affect agriculture to any appreciable extent," and also "probably entirely beneficial from our present point of view" by the Rev. Henry Slater (2, p. 248). This is not correct, for this bird is very common in parts of Britain, and is not only very harmful to game and poultry, but the farmer suffers considerable loss by its attacking lambs and pecking out their eyes. The work of the Hooded Crow in the poultry-yard is best expressed in the words of Mr. W. Swaysland (7, p. 102, vol. ii.): "Its powers of mischief in respect to the poultry-yard during breeding time are so exceedingly well developed that as late as the year 1835 the different local authorities of Shetland and Orkney were in the habit of paying *2d.* for each crow killed in their districts."

Although liking the littoral, the Royston Crow, as it is also called, occurs far inland. In East Kent their ravages amongst poultry and lambs are well known. A certain amount of insect

food and shore garbage is taken by them, but all evidence points to their injurious nature, even on the coast, as destroyers of mussels and cockles.

The Jackdaw (*Corvus monedula*, Linn.) is a great wireworm and insect destroyer, and if it does a little injury to cherries and other fruit in dry seasons, and takes a few eggs and now and then fowls' food, it nevertheless must be looked upon as beneficial, as far as evidence goes at present.

The Magpie (*Pica rustica*, Scopoli) affords a most difficult problem. It is an arrant thief: it will take young chicks and eggs, it strips rows of peas, and will even attack young and sickly stock. But as a means of keeping the blackbird and the woodpigeon in check it is said to be of the greatest value, and as the two latter are serious enemies of man, it might be wise to suffer annoying loss for more permanent good. It is doubtful, however, if it does as much good as is supposed in the case of the woodpigeon, for it is those pigeons that migrate to us from the Continent that do most harm, and not our home-bred birds, which are considerably larger. The opinion, however, held by some authorities is that it is beneficial, whilst others practically interested wish to discourage it.

Of the Jay (*Garrulus glandarius*, Linn.) it seems still more difficult to judge, for on one hand the Rev. H. Slater (2, p. 248) says, "I would never shoot a jay," and on the other Fred Smith says (3, p. 7) "he should be kept down." On the one hand we have the opinion of a skilled ornithologist, on the other of a skilled grower. It is certainly harmful in fruit plantations, spoiling countless numbers of the best coloured apples, destroying nuts, plums, and frequently, like the magpie, whole rows of peas. In return the Jay takes many blackbirds' eggs, slugs, snails, cockchafers and other insects, mice, and young birds. It seems that they do no damage in game preserves, and the gamekeeper is wrong in his persecution of them from his own point of view; but according to Mr. F. Smith, it is a pity they are not more persecuted when the preserves are near fruit.

Except that they are excellent eating, nothing good can be said for the Woodpigeon or the Stockdove. Moreover, the former are very much on the increase, and the yearly bands of robbers that come to us from the Continent of Europe in winter and stay into early spring cause endless damage to the

farmer, eating off whole fields of cabbage, attacking grain, pulse, clover, and tops of turnips; later woodpigeons take cherries and gooseberries.

Many years ago the Earl of Haddington made investigation into the food and habits of the Woodpigeon; the results showed it to be very harmful to agriculture. Gilmour (16) says "that as years go by the character of the Woodpigeon does not improve, but his destruction of clover and grain far outweighs any benefit he may effect."

In the woods, too, they do harm devouring buds, catkins, seeds, and breaking the leaders of firs and spruce. "This bird should decrease in numbers," says Mr. Cecil Hooper, "for it is good food and worth 1*s.* a brace." Yet we neglect this matter, and still go on persecuting those keen farmers' friends, the Lapwings or Green Plovers, by taking their eggs, set and sound alike.

The Stockdove, where it occurs in numbers, appears to be as bad as the Woodpigeon.

The Turtle Dove (*Turtur communis*, Selby), a summer visitor, does some harm to fields of tares and peas, but is seldom sufficiently abundant to occasion any serious loss to the farmer. The forester suffers from this bird in the late spring, when it eats up seedlings, and again when it alights in flocks on sowings, and does much damage, so we are informed by Fisher (8). There is no doubt that the Doves take weed seeds, but many of these are passed whole. The good they do cannot then be said to balance the amount of damage caused by them to the farmer and forester, and their numbers should be kept in check.

The Lapwing, Green Plover, or Peewit (*Vanellus cristatus*, Linn.) is well known and still common, but in many districts its numbers have been sadly reduced. This is due entirely to the ruthless destruction of the eggs. It is said that high prices are paid for the eggs as articles of diet. We venture to disagree—high prices are charged in shops for them, but low prices are given for them to the collectors. The reason is that often the greater number collected are set and thus valueless. The result of this collection is that many insects injurious to crops multiply enormously. There is no bird more beneficial to the cultivator than the Lapwing. Its food consists entirely of wireworms, leather-jackets, surface larvæ, snails, slugs, and

many other injurious animals. The good done by the Lapwing cannot be overestimated: no one has said or can say a bad word against it. In spite of this, people are allowed to collect the eggs wholesale, and the demand increases, and, in consequence, in many parts the bird is decreasing. With this decrease goes a concomitant increase of wireworm and other grubs.

Surely where, as in this case, we have a unanimous opinion, the somewhat useless and seldom-enforced Wild Birds Protection Acts might be employed, so as to make it not only illegal to take the eggs but to offer them *for sale* in shops.

When we come to consider the Finches (Fringillidæ), of which twenty-nine are recorded as British, the matter becomes simpler, for there is no doubt that when the common species become very abundant they are destructive. Eleven of them are very rare. Six or seven only can be looked upon as harmful species. There is not the least doubt, nevertheless, that all the Finches do some good, but it does not make up, it appears, for the amount of loss they cause. Most authorities agree that two are so pernicious that they must be destroyed, namely, the House Sparrow and the Bullfinch. That Finches do some good we are all bound to acknowledge, for they mostly feed their nestlings on insect life. Much of that insect life consists of injurious species, but by no means all, for lady-bird larvæ, etc., are also taken, so that the good the Finches do by taking insects must to some extent be discounted. Weed seeds are also greedily devoured, but many of these are passed whole, so that the birds act as distributing agents. The good then that such birds do is insignificant compared with all the harm that is constantly being reported.

The Sparrow (*Passer domesticus*, Linn.), or Avian Rat as Mr. Tegetmeier fitly describes it, was no doubt a feeder on wild seeds, but as the Rev. H. Slater states, "it has now attached itself to man, influenced by his untidiness and wastefulness, until it has become the worst of all his pests."

Whether man's untidiness had anything to do with the matter may or may not be the case, but that it is one of his worst pests in many parts of the world is only too well known. Yet what trouble it took to introduce this bird into America, and what would they now give to be free of it! Nevertheless, there are believers in the Sparrow, for Mr. J. P. Nunn (4, p. 1) says: "There can be no doubt that the sparrow

is a most omnivorous feeder, and at certain seasons does some damage: nevertheless, all the damage is fully repaid by the good it does." Later, he says: "It must be admitted by all those that are at all observant that they are great insect-eaters and that their brood are chiefly reared on insects."

Mr. J. H. Gurney and Colonel Russell (9) have shown, on the other hand, that 75 per cent. of sparrow food is corn, 10 per cent. weeds, 4 per cent. green peas, and only 6 per cent. insects and 5 per cent. other matter. Young sparrows do not have an exclusive insect diet, for they are fed chiefly upon young corn in the milky state. In flower garden as well as in field they are a veritable plague. One would think sparrow clubs, as recommended by the Board of Agriculture, would have some effect, but in the writer's village 4,000 odd sparrows were brought in in 1905, and 6,000 in 1906, yet they are as plentiful as ever.

That there is something to be said in favour of the Sparrow as a destroyer of chafers, crane flies, moths, etc., we know, but the enormous loss in corn, crop seeds, flowers, etc., besides the damage they do to thatch, is so great, it is necessary to take all possible steps to destroy them.

The Bullfinch (*Pyrrhula europæa*, Vieillot) has nothing to its credit side, according to all practical men. But again dealing from the farmer's point of view, the Rev. H. Slater (2, p. 24) says it is "a perfectly harmless and altogether desirable neighbour, as it feeds on hedge fruits, seeds of docks, thistle and other weeds." Again, we must repeat, man can keep down his weeds. It seems almost impossible to keep birds from attacking buds of trees. A single bullfinch will do more harm in a plantation of fruit than all the rest of the birds put together. For six months they live entirely on fruit buds, and as they come from the woods in autumn and continue till March the loss they occasion can be well estimated. All connected with fruit culture agree that they must be summarily dealt with by trap, powder and shot. Mr. Slater's suggestion of "throwing stones" to frighten them away can scarcely be treated seriously.

It has been stated that they feed their young on insects, but they are really fed, as Mr. C. F. Archibald says (5, p. 81), "on seeds softened by the parent."

In woods and forests they are equally harmful, for there they feed upon the buds of beech, larch, hawthorn, etc.

There is no better judge of the economic value of birds than Mr. F. Smith, and he shot no less than 285 bullfinches in his fruit plantations in the winter of 1905, and yet they still come from the woods. At Wye the sparrow club received 147 in the winter of 1905–6, and no less than 200 in the past winter, yet we still have some doing damage to the fruit.

The Chaffinch (*Fringilla cœlebs*, Linn.) is not generally thought to be harmful. In an article on the bird in *The Board of Agriculture Journal* the writer says "many fruit-growers and all who are careful observers regard the chaffinch as one of their best friends," and concludes by saying: "In France and Germany the chaffinch is regarded as a useful friend to cultivators, especially by fruit-growers." We are not aware of this in France, Belgium, or Holland. Ritsema Bos (10, p. 64) says: "It does a great deal of damage in cornfields by picking the seeds out of the soil after they have been sown, but does not take the grain from the ear; it also eats young seedlings: but valuable services more than counterbalance the harm it does." Mr. F. Smith tells us it is a great nuisance as a disbudder of fruit, especially after a frost, and they squeeze the blossoms to extract honey from them later on. Gardeners generally complain of its depredations, especially in regard to attacking sprouting seed of Brassicæ. The forester also complains of the chaffinch feeding on coniferous seeds and biting off the young cotyledons and leaves of beech and conifers. Archibald (5, p. 78) refers to the attack on Scotch firs, etc., and says "at times it does considerable damage to young turnips, radishes, and similar crops."

In return the Chaffinch takes a few caterpillars, mainly for its young, flies, aphides, including the woolly aphis, and also seeds and beechmast, the seeds including those of many weeds, especially Knot-grass (*Polygonum*). There seems so much difference of opinion in regard to this finch that it is probably best left in its present condition, but any undue increase must of necessity be checked by shooting the birds after their nestlings are mature.

The Greenfinch (*Ligurinus chloris*, Linn.) where abundant is worse than the Chaffinch. It is a great destroyer of fruit blossom, it picks hops to pieces, it eats the seeds of ripe

strawberries. Flocks fly to fields sown with sainfoin, turnip, etc., and clear out all the seed; they also fly to new sowings in forests and do endless harm. In return they feed on weed seeds and feed their young on insects of all kinds.

The Hawfinch (*Coccothraustes vulgaris*, Pallas) is one of those birds about which there is sure to be difference of opinion in regard to killing it, owing to its supposed rarity. In reality it is not only very common in many parts of Britain, but is very much on the increase: even as far back as 1892 this was noticed by Archibald (5, p. 80). That it does a large amount of damage to green peas every one acknowledges; it also attacks apples and pears for the pips; whilst damsons and nuts suffer largely from it. Certainly it takes large numbers of caterpillars and other insects, chiefly for its young. Mr. Archibald considers it a pity to destroy it owing to the latter fact, but those who suffer from its inroads think differently. There certainly does not seem any evidence to entitle it to the protection afforded it by some county councils.

The Linnet (*Acanthis cannabina*, Linn.) is often harmful in hop gardens with the Greenfinch. When present in large numbers it becomes a great pest, feeding on turnip, swede, rape, cabbage seed, and also where the crop is grown for seed. Flax and hemp are especially destroyed. Numerous weed seeds are also eaten and numerous insects. The general opinion seems to be that the bird may be encouraged except in occasional circumstances.

Neither of our two common Buntings—the Yellow-hammer (*Emberiza citrinella*, Linn.) nor the Corn Bunting (*E. miliaria*, Linn.)—are of any special economic account: both take a certain amount of corn, but feed mainly on weed seeds and insects.

The Skylark (*Alauda arvensis*, Linn.), although it takes a certain amount of corn, has the balance in its favour, for it is most helpful as an insect-checker, including wireworms. Charlock, knot-grass, and chickweed seeds are eaten in large quantities. Archibald (5, p. 73) says: "Seed-corn, especially autumn-sown wheat, both before and after sprouting, possesses great attractions for it, but it is only in exceptional cases that the crop is materially injured in consequence." According to Slater (2), very little grain is taken, and then only that left uncovered. It is in hard weather that larks become a serious nuisance, for they will then strip whole fields and gardens of winter greens.

Of the Warblers (of which nineteen are recorded as British) three only need be discussed, namely, the Blackcap (*Sylvia atricapilla*, Linn.), the Whitethroat (*S. cinerea*), and the Garden Warbler (*S. hortensis*, Bechstein); the remainder, if not actively beneficial as aphis and other insect destroyers, are at least innocuous.

The Blackcap does any amount of harm in the garden and fruit plantation. Mr. F. Smith (3) tells us that "a family of blackcaps in a cherry orchard will commit great havoc." Mr. Archibald (5) mentions it as being devoted to currants, strawberries, raspberries, and cherries, whilst, like the Whitethroat, it opens pea-pods. "Its visits to the garden, therefore," he says, "cannot be considered altogether desirable." It is also known as the Fig Bird, as it consumes that fruit in enormous quantities. The spiders, insects, etc., that it also eats do not apparently make up for the harm it does.

The Whitethroat is as bad in habits, and should be rigidly excluded from plantation and garden; and the same is said of the Garden Warbler. Fortunately, both the latter are not sufficiently common to do very much harm. Mr. C. Hooper (1) records the Whitethroat also as attacking green gooseberries.

Of the three recorded Flycatchers the Spotted Flycatcher (*Muscicapa grisola*, Linn.) is the only common one. It is most beneficial, feeding solely upon insects, including many of those which devour our crops and fruit. It seems that all accusations against them fail when carefully examined. Their encouragement and protection should thus be rigidly enforced.

Of other summer migrants the Cuckoo (*Cuculus canorus*, Linn.) is a decidedly useful bird, and does no harm. It is the only powerful natural check we have on such insect pests as the hairy caterpillars of the lackey and brown-tail moths, and other similar depredators of our woods and plantations.

As ant-destroyers we have the Wryneck (*Iynx torquilla*, Linn.), too scarce, unfortunately, to do much good in lessening their numbers, and the Woodpeckers (Picadæ).

The latter are too few by far, for they do good in endless ways in woods and plantations and seldom do any serious damage. At one time they have been considered harmful, at another beneficial. In the orchard they seem to be in favour, for they certainly destroy wood-boring insects. In the forest, authors and foresters seem to disagree as to their utility. According to

Bechmann (11), they were considered very harmful by pecking holes in trees, and *2d.* per head was offered in Germany for their destruction. But in the same year Bechstein is said to have considered them useful, and by degrees foresters began to look upon them as beneficial, and so on for years opinions have been for and against them. In 1881 so great was the damage done by Woodpeckers to telegraph poles in Germany that instructions were sent that all holes in the poles had to be filled with wood plugs and cement.

That they do harm by pecking into trees, by destroying seeds, and by girdling trees, we have undoubted proof; but, on the other hand, it is acknowledged that they do much good by destroying large numbers of injurious insects which man has difficulty in doing. Fisher (8) sums up by saying: "The result of investigations into the utility of woodpeckers tends to show that these birds, by their activity in the destruction of insects, play a most useful part in nature, and should therefore be protected by foresters."

Few birds have more friends than the family of Tits (Paridæ). On the farm and in the forest they do no harm at all. In the orchard and garden the Blue Tit (*Parus cæruleus*) and the Great Tit (*P. major*) do some slight damage. The former attacks ripe apples and pears, pecking near the strig and so spoiling them for market; the Great Tit does the same, and takes a few nuts. Recently the Blue Tit has been reported as attacking the buds of the Monarch Plum. This is probably to get at the mites (*Eriophyes pruni*) which hibernate in the buds. In spite of these few errors in their ways, all seem agreed that the Tits do much good, for they hunt summer and winter for insects. The mussel scale, codling moth, woolly aphis, etc., are their especial favourites, and the good they do in this way is incalculable. According to Mr. F. Smith, it is the Great Tit, or Ox-eye, that takes the plum buds in Kent; but in Worcestershire Mr. G. Hooper states it is the Blue Tit.

The Cole Tit is also recorded as doing some damage by attacking the buds of the black-currants, and eats the embryo bunches of fruit. Is it wise to take this indictment against the tits without further observations as a purely destructive act? Careful observers have shown that the bunches of unopened apple and pear blossom that the tits peck contain insect larvæ, and it may be that they do so in plums and

currants to obtain the mites (*Eriophyes*) that live there. In fact, the only injurious act we have *proved* against these little birds seems to be that of pecking the base of ripe pears and apples. This may easily be prevented by planting a few rows of sunflowers in the plantations so that they blossom about the time the fruit is ripening. Mr. F. Smith has found that by so doing the tits go to the sunflowers and leave the fruit alone.

The consensus of opinion of practical men and ornithologists is so strongly in favour of the Paridæ that we may safely say they should receive all the protection we can give them.

The Wagtails (Motacillidæ), with which are included the Pipits (*Anthus*), need not concern us, for they are universally accepted as beneficial by virtue of being great destroyers of insects, slugs, water snails, worms, etc., and help materially in keeping down many noxious creatures, such as the water snail (*Limnæus truncatulus*) that is the secondary host of the liver fluke of sheep.

Unfortunately, from this useful family we have to turn to the Thrush family, or Turdidæ. As far as the farmer, forester, and gamekeeper go they have no cause for complaint, nor has even the gardener except when his fruit is ripening. The fruit-grower, however, has endless loss caused by this family of birds. The Blackbird, Thrush, and Missel Thrush are the most important.

Mr. Cecil Hooper voices the general opinion when he says (1, p. 78) that "the Blackbird, as far as the fruit-grower is concerned, is the blackest of thieves."

It is incredible how the Blackbird has increased in recent years. Although hundreds have been shot in plantations, it seems to make no difference. Mr. John Riley, of Putley Court, near Ledbury, killed hundreds in his plantations, and he tells me they are still far too numerous. Mr. C. Hooper records a Bedfordshire grower having trapped last year five hundred, and yet they still persist in large numbers. Mr. F. Smith (3, p. 4) records that for the last seven or eight years he has trapped over a thousand blackbirds and thrushes yearly. "This year (1906), from the quantity left to breed," he says, "I shall have to destroy at least two thousand to keep them at all within bounds; that is, on about two hundred acres of fruit." The sparrow and rat clubs in East Kent include the blackbird in their lists. At Elmsted 469 were brought in last year, at

High Halden 291, at Wye they are included with sparrows and linnets (green), and numbered, I believe, 700. Yet in these places they are still in great numbers. This is to some extent due to partial migration. Annually great flocks arrive in the eastern counties, and then proceed farther south and west. Owing also to their rapid rate of reproduction, often having three or four nests in the year, it will be all man can do to keep this pest in check.

The damage in recent years to fruit has been enormous. They do not seem to be particular, for ripe and ripening cherries, strawberries, raspberries, red and white currants, and plums are cleared off wholesale. Recently apples have been badly attacked, always the best and brightest fruit spoiled by their pecking holes in it. This wholesale attack takes a large slice of the fruit-grower's profits from him. Those who wish the bird protected say in support that it devours large numbers of beetles, caterpillars, snails, etc., and that its song is beautiful.

Every one interested in the cultivation of fruit is agreed that the Blackbird is a veritable plague; the good it does is slight, and there seems not the least doubt that, with the Bullfinch, it should be destroyed. Moreover, if killed in the winter, they can be utilised as food, for they form no unpalatable dish.

With regard to the Thrush, there are extenuating circumstances, for it is one of the chief means by which snails are kept in check, and snails are very difficult for man to destroy. The "judge" must recommend the Thrush to mercy. But as regards a destroyer of fruit, it is almost as bad as the Blackbird. It is not so bad with the apples, it is true, but with other fruit it vies with its relation as a destructive agent.

Mr. Hooper tells us that "even after large numbers have been killed, fresh arrivals take the place of the slaughtered birds." All the young thrushes reared in this country are said to emigrate as soon as they can, and are then followed by their parents, so that many parts of the kingdom are bereft of this bird from October to January. But there is no doubt that many remain over the winter. In spite of the damage it does to fruit, we must record the fact that for nine months the thrush does good, feeding on snails, slugs, insects, worms, and berries. Those that are permanent suffer severely in cold winters, long before the blackbirds, and they do not seem to increase, as does the latter bird.

Every one interested in the economic aspect of bird life seems agreed that they should be kept in check, but that wholesale slaughter is not essential, as it is with the "blackest of thieves."

The Missel Thrush (*Turdus viscivorus*, Linn.) is not so common as the former, but its work in the orchard and fruit plantation is far worse. In Kent growers consider it one of the worst birds. It takes even black currants, which most birds avoid. Its nest is frequently made in gooseberry bushes in plantations in that county. Its other food besides fruit consists of various wild berries, grain, seeds, caterpillars, beetles, slugs, snails, and worms. The farmer gets some benefit from it, but the fruit-grower seems certainly entitled to complain of its destructive powers and keep its numbers down.

Our other members of this family—the Fieldfare, the Redwing, and the Ring Ouzel—call for no comment, save the Chats, such as the Wheatear, Stonechat, Whinchat, and Redstart, Robin, and Nightingale, all of which do good.

It is pleasing to turn to the Starling (*Sturnus vulgaris*, Linn.). In spite of its severe depredation on cherries, damsons, plums, apples, pears, and raspberries, growers are all agreed that it is a valuable friend on the farm.

John Gilmour (16) says of this bird: "A perusal of the record of his food will show he comes out of the examination with flying colours, and must be regarded most certainly as a friend of the farmer."

The Rev. Henry Slater (2) says of it: "Normally one of the most useful birds we have, from an agricultural point of view." Horticulturists do not agree with this statement, for it is an undoubted pest in fruit districts. On the farm and in woodlands, however, the good the starlings do is inestimable. They are acknowledged on all sides as being great wireworm, leather-jacket, and other terrestrial grub eaters; they also devour slugs, and pick the keds and ticks off the backs of sheep. The Rev. Henry Slater says: "I am not sure, however, whether its numbers are not increasing beyond the normal, but cannot point to any tangible damage which over-population is driving them to commit."

The general opinion may be summed up that the Starling is most beneficial to the farmer and stockbreeder, and should be encouraged, but that in fruit districts its numbers should be kept down.

The family of Gulls (Laridæ) may on the whole be said to be beneficial from the farmer's point of view.

Those that we find inland are the Common Gull (*Larus canus*, Linn.), the Herring Gull (*L. argentatus*, Gmelin), and the Brown-headed Gull (*L. ridibundus*, Linn). They may very frequently be seen a long way from the sea in winter and spring, following the plough, and taking all kinds of surface larvæ and grubs that are thrown up with the soil.

It has been said that the Brown-headed Gull, which breeds in colonies locally, is destructive to young trout and salmon, but the Rev. Henry Slater, who investigated this matter for the Cumberland County Council, tells us that he failed to find the least evidence of their doing so. This gull not only takes grubs, but also adult chafers and moths. Now and again the Common Gull, which does not breed south of the Solway, will take grain, and so will the Herring Gull, and both have been found to pull up young turnips and destroy them ; nevertheless, it is well known that insects, slugs, and worms form their chief food when inland. Two Laridæ only can be placed on the "black list," namely, the Lesser Blackback (*L. fuscus*, Linn.), which does some harm to inland game, and the Great Blackback (*L. marinus*, Linn.), which is recorded as attacking sickly lambs, and even sheep. The farmer seems certainly justified in keeping the latter in its proper place by the sea-shore, where it destroys garbage.

Game-birds must be looked upon in rather a different light. Of the two families, the Phasianidæ and the Tetraonidæ, the latter may be excluded in regard to any damage done, unless it is by the Capercaillie (*Tetrao urogallus*, Linn.), which was exterminated in the eighteenth century and re-introduced into Scotland in 1837, and which is now especially common in the fir-woods of Perthshire. Fisher mentions it as injurious in nurseries and cultivations of conifers in winter and spring by biting off buds and young shoots ; it also damages birch buds and cones, the cock being more injurious than the hen. But it also does good by destroying insects, and its value for sport and food must discount any damage it does.

Some farmers complain of Pheasants and Partridges. Certainly the former scratch up some seed-corn and cause minor inconveniences, but the complainers must not forget that they do an enormous amount of good by destroying

various grubs, and those who preserve the same are doing more good than harm to the farmer, as well as providing themselves with sport. Game-birds may well be protected, not only from the sportsman's point of view.

There are many other birds which must be watched, but which at present are of no special economic importance.

Taking no account of sentiment, we may fairly say that there are a few birds, such as the Sparrow, Bullfinch, Blackcap, Sparrow Hawk, and some Finches, which must be found guilty, and many, such as the Kestrel, Owls, Lapwing, Tits, most Gulls, etc., which may be acquitted. Unfortunately very many more, such as the Jackdaw, Rook, several Warblers, and Finches, upon which must be pronounced the verdict of "non-proven," on account of the very conflicting evidence.

No satisfactory decision can be arrived at concerning these until we have much more evidence to guide us. The only way this is likely to be achieved is by the appointment of a departmental committee, who could collect evidence from all parts of the country and from all points of view, and further systematic work on the food contents of birds' stomachs and crops.

One great thing might be done in advising the condensation of the Wild Birds Protection Acts into one homogeneous whole and the drafting of more definite information to county councils, so that their scheduled lists might be more consistent with our present knowledge than they are now.

The economic value of birds must be considered from all points of view in a very broad spirit, and before we can say anything definite regarding the majority of them the subject must be studied in the field on a much sounder basis than has yet been done.

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THE PINEAL GLAND

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In a sagittal section of the human brain one sees, projecting upwards and backwards from the thin roof of the thalamencephalon or 'tween-brain, and lying deep down in the great median fissure which separates the two cerebral hemispheres from one another, a small solid body of about the size of a cherry stone. This body is known to human anatomists as the "conarium" or "pineal gland"—names which it received from the older writers on account of a supposed resemblance to a pine-cone, while the more general term "epiphysis cerebri" has been applied by students of comparative anatomy to outgrowths of the brain-roof occurring in a corresponding position throughout almost the entire vertebrate series.

The function of this enigmatical organ had for long been a favourite subject of speculation before the introduction of scientific methods in the nineteenth century made it possible to attack the problem with any hope of success.

In the first half of the seventeenth century the great French philosopher Descartes bestowed a very large amount of attention upon the structure in question, which, indeed, may be said to have formed the organic centre of his systems of physiology and psychology. As Huxley has said: "The fame of Descartes filled all Europe, and his authority overshadowed it, for a century," and the remarkable views which he held upon this particular subject were no doubt very largely responsible for the special interest which has for so many years attached itself to the pineal gland. It is, therefore, perhaps worth while to devote a little space to the consideration of Descartes' theories.

In *Les Passions de l'Âme*, published in 1650, Descartes discusses the question of the seat of the soul, and concludes that, although the soul is united with the whole body, yet it exercises its functions more particularly in a little gland placed in the middle of the substance of the brain and suspended above

the passage by which the "spirits" of its anterior cavities communicate with those of its posterior cavities, in such a manner that any movement in the gland will alter the course of these spirits, while at the same time any alteration in the course of the spirits will affect the movements of the gland.

There can be no doubt that the gland here referred to, though not mentioned by any special name, is the pineal gland or conarium of human anatomists, although the author's limited acquaintance with the structure of the human brain caused him to represent it as lying inside instead of outside the brain-cavity.

Descartes goes on to explain that the reason which induced him to regard this gland as the place where the soul immediately exercises its functions is that the other parts of the brain, as well as the external organs of sense, are all double, while our thoughts are single, *i.e.* we only have one single and simple thought of one and the same thing at the same time. Hence the double impressions which come from the paired organs of sense —such as the two images from the two eyes—must be able to unite into one before they reach the soul, or else we should see two objects instead of one; and this union is supposed to take place in the pineal gland by the mediation of the spirits which fill the cavities of the brain.

In a later essay, entitled *L'Homme*, Descartes elaborates his peculiar system of physiology, and it is most curious to note the enormous importance which he attributes to what he terms "the little gland H," shown in his charmingly quaint illustrations as a conspicuous pear-shaped body lying in the middle of the brain, or sometimes simply in the middle of the head, the rest of the brain being omitted.

In the seventeenth century there were commonly to be seen in the royal gardens or parks in France elaborate mechanical toys worked by means of water carried in pipes from a central spring to the various figures or other pieces of mechanism which it was desired to set in motion. These contrivances seem to have furnished Descartes with his principal ideas on the physiology of the nervous and muscular systems. Thus he compares the "external objects" which act upon the sense-organs, and thereby cause the body to execute movements of various kinds, to strangers who enter unawares into one of the surprise grottoes, and by treading upon the concealed machinery set the figures in motion. The water which works the apparatus is

supposed to be represented in the human body by the "animal spirits," described as a kind of "subtle gas," or rather a "very active and very pure flame," originating in the heart and deriving its energy from the heat of that organ. This is mingled with the blood and carried by an artery to the pineal gland, where it is separated again and poured out as from a fountain into the cavities of the brain. The inner surface of these cavities is supposed to be porous, and the pores are supposed to lead into the nerve fibres, which are represented as being hollow tubes down which the animal spirits flow. Thus what we now call motor impulses were thought by Descartes to be due to the actual movement of a quantity of fluid from the brain cavity through the nerves to the muscles, which they cause to move by rendering them turgid.

Meanwhile the soul sits in the pineal gland, like the engineer of the water-works in the midst of his pipes and fountains, and exercises a kind of general supervision—influencing the animal spirits in various ways; suffering pain when things go wrong and rejoicing when they go right.

The general belief in the fundamentally azygos or unpaired nature of the pineal gland, to which Descartes attributed such unique importance, was destined for many years to prejudice opinion as to the true character and morphological relations of this organ. Moreover, our knowledge was for a long time derived almost exclusively from the human subject, in which the pineal gland exhibits the highest degree of secondary modification, and has lost almost every trace of its primitive character; and it was not until the problem was attacked by comparative anatomists that any real advance was made in this direction.

In 1872 Leydig, apparently for the first time, called attention to a "parietal sense-organ" which he had discovered in lizards (*Lacerta*) and blind-worms (*Anguis*). Ten years later Rabl-Rückhard began to speculate on the possible homology of this organ with the median eyes of arthropods, and in 1884 the same author called attention to the unpaired foramen which exists in the parietal region of the large fossil reptiles of the secondary period, *e.g.* ichthyosaurians and plesiosaurians, and suggested that this foramen might have contained the modified distal extremity of the pineal organ, in the form of a sense-organ which served to warn its possessor of the intense heat of the tropical sun. In the same year Strahl also maintained that

the parietal organ, to which he gave the name "Leydig's body," was a portion of the epiphysis constricted off from the remainder. Again in 1884 Ahlborn came to the conclusion that the epiphysis or pineal gland is the vestige of an unpaired eye, analogous to the unpaired eye of tunicates and perhaps also of *Amphioxus*, basing his conclusions mainly on his own classical researches on the brain of the lamprey.

So far, however, the evidence in favour of the visual character of the parietal or pineal sense-organ had been but slight, and it was not until 1886 that this view received much support. In that year H. W. de Graaf published a short paper in the *Zoologischer Anzeiger* on the Anatomy and Development of the Epiphysis in Amphibia and Reptiles. In this paper the author maintains that whereas in the Anura the extremity of the epiphysis becomes constricted off to form the "gland of Stieda" or "Stirndrüse," lying outside the cranium in the middle of the dorsal surface of the head, and exhibits no eye-like character, in *Lacerta* and *Anguis*, on the other hand, the same organ acquires a distinctly eye-like structure comparable to that of the eyes of certain invertebrates. He further calls attention to the parietal foramen in the extinct labyrinthodonts of the Carboniferous, Permian, and Triassic epochs, and concludes that the epiphysis in the ancestors of living animals must have played a very important part as a sense-organ. This paper, although only of the nature of a preliminary communication, contains a striking figure of the pineal or parietal "eye" in *Anguis fragilis*, to which no doubt was due in large measure the interest which it excited. The author's complete memoir, with a still more beautiful figure of the organ in question, was published in the same year. In the meantime the matter had been taken up in England by Baldwin Spencer, who, while giving full credit to de Graaf for his work, greatly extended our knowledge of the subject by the investigation of numerous lacertilian types and of the remarkable reptile *Sphenodon* (*Hatteria*), in which the "pineal eye" still exhibits a very high degree of organisation. Spencer's beautifully illustrated memoir (published in *The Quarterly Journal of Microscopical Science* for October 1886) naturally served to greatly intensify the interest which had already been aroused on this subject, and from this time onwards the literature dealing with the pineal apparatus and the parts of the brain associated therewith increased rapidly.

So far it had been generally supposed that the "eye" was an unpaired median structure formed by the constricting off of the distal extremity of the pineal outgrowth or epiphysis, and, according to Baldwin Spencer, the constricted portion of the latter actually persists in some cases (e.g. *Sphenodon*) as the nerve of the pineal eye. Strahl and Martin in 1888, however, showed that the nerve really originates quite independently, a conclusion shortly afterwards confirmed by the researches of Béranek upon the development of *Anguis*; while Gaskell, in 1890, appears to have been the first to raise his voice against what may be termed the cyclopean dogma of the "median eye." Gaskell argued strongly in favour of the paired character of the pineal sense-organs in the larval lamprey; but, unfortunately, the startling character of his theory as to the origin of vertebrates, which he endeavoured to support by this argument, seems to have prevented his observations from receiving due attention. Gaskell's views as to the arthropod-like structure of the pineal eye have, indeed, not been confirmed by subsequent investigators; but his opinion as to its paired character has been strongly supported from several directions. The work of Charles Hill (1891 and 1894) on the development of paired epiphysial outgrowths in teleost and ganoid fishes, that of Locy (1893-4) on the development of accessory optic vesicles in elasmobranchs, that of Cameron (1903 and 1904) on the paired origin of the epiphysis in Amphibia and birds, that of Dendy (1899 and 1907) on the development of the pineal organs in *Sphenodon* and on the corresponding organs in *Geotria*, all tend to show that the pineal eye, though now apparently median, is in reality one member of an original pair. This question cannot, however, as yet be regarded as finally settled; for although most writers now admit the double character of the organs in question, some maintain that they do not form a pair, but were *primitively* developed one behind the other, as they actually appear in many cases at the present day, and have not acquired their antero-posterior relations by secondary displacement, as we believe to be the case.

We cannot conclude this brief historical introduction without referring to the excellent researches of Studnička, who since 1893 has taken the lead in the investigation of the minute histology of the pineal or parietal organs, and who has also given us an admirable general account of these organs in

Oppel's *Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbelthiere* (1905).

It is only within the last few years that our knowledge of the fore-brain and its derivatives has advanced sufficiently to enable us to formulate with any degree of precision the morphological relationships of the pineal outgrowths. For this purpose we may accept, at any rate provisionally, the neuromeric subdivision of the brain which we owe mainly to the embryological investigations of Locy and Hill. It appears tolerably certain that the vertebrate brain is built up of no less than twelve neuromeres (fig. 1, *N.* 1-12), which can be recognised with greater or less distinctness in the embryo and indicate the primary metameric segmentation of this region. Of these neuromeres the first three give rise to the fore-brain, the fourth and fifth to the mid-brain, and the remainder to the hind-brain. In the fore-brain the first neuromere (*N.* 1 ; *Pros.*) gives rise to the prosencephalon ("telencephalon" of German authors), from which the cerebral hemispheres (*C.H.*) are developed, while the second and third (*Thal.*) form the thalamencephalon (or diencephalon), with which alone we are at present concerned. At a very early stage in development a pair of outgrowths from the second neuromere form the optic vesicles of the ordinary paired eyes, while the third neuromere probably gives rise to the "pineal" or "epiphysial" outgrowths (*Ep.* 1, *Ep.* 2), which appear at about the same time on the roof of the thalamencephalon. In many fishes, and again in Lacertilia and *Sphenodon*, it is easy to recognise two of these pineal outgrowths, which may either lie one behind the other *ab initio* (*e.g.* in *Petromyzon*), or may present more or less clear indications of a bilaterally symmetrical arrangement (*e.g.* teleosts, *Amia*, *Sphenodon*), suggesting a serial homology with the ordinary optic vesicles. In the higher vertebrates one of these two outgrowths is either completely suppressed or merged in the other at a very early date, so that the "epiphysis" or "pineal gland" may appear to be single and median even in origin.

Immediately behind the fore-brain the anterior limit of the mid-brain is marked by the posterior commissure (*C.P.*), which lies just behind the pineal outgrowths, and at a short distance in front of this lies the superior or habenular commissure (*C.H.S.*), a transverse band of fibres which connects together the two habenular ganglia lying on the optic thalami, and

which appears to be quite constant throughout the vertebrate series.

It is now tolerably certain that the two habenular ganglia are primarily related to the parietal or pineal sense-organs (developed from the pineal outgrowths), with which they are still connected in some cases (*e.g.* lampreys) by nerve-fibres. One of the two pineal outgrowths, forming the so-called "stalk"

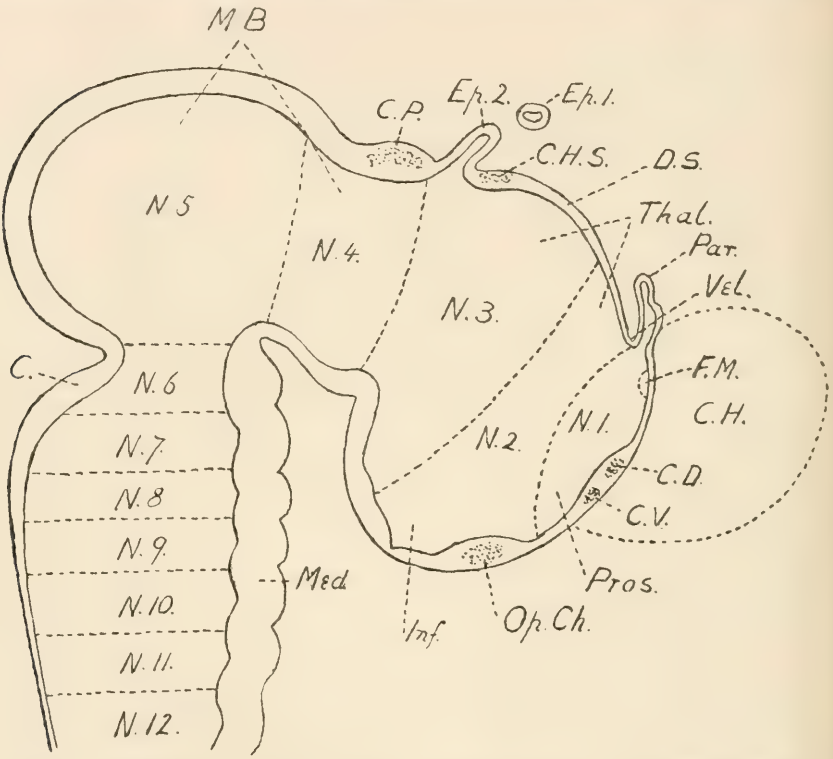

FIG. 1.—Diagrammatic sagittal section through the brain of a typical vertebrate embryo (the pineal organs as in Lacertilia).

C., cerebellum; *C.D.*, dorsal (mantle) commissure; *C.H.*, cerebral hemisphere; *C.H.S.*, superior (habenular) commissure; *C.P.*, posterior commissure; *C.V.*, ventral (anterior) commissure; *D.S.*, dorsal sac; *Ep.* 1, anterior epiphysial outgrowth (pineal eye); *Ep.* 2, posterior epiphysial outgrowth (pineal stalk); *F.M.*, foramen of Monro; *Inf.*, infundibulum; *M.B.*, mid-brain; *Med.*, medulla; *N.* 1-12, neuromeres; *Op. Ch.*, optic chiasma; *Par.*, parapHysis; *Pros.*, prosencephalon; *Thal.*, thalamencephalon; *Vel.*, velum transversum.

(with or without a terminal enlargement), remains connected with the brain-roof either permanently or at any rate for a long time, at a point which lies between the superior and posterior commissures. From each of the habenular ganglia

a bundle of nerve-fibres, known as Meynert's bundle, or *tractus habenulo-peduncularis*, or *fasciculus retroflexus*, runs backwards and downwards to the base of the brain through the substance of the corresponding optic thalamus, and, as we shall see later on, the condition of these fibre-tracts in the lampreys affords most important evidence with regard to the paired nature of the pineal organs.

In front of the superior commissure the thin epithelial roof of the thalamencephalon, in the embryo, is usually more or less strongly bulged outwards to form the "dorsal sac" (*D.S.*), at the anterior limit of which a transverse fold of the ependyma, known as the velum transversum (*Vel.*), commonly projects into the brain-cavity and marks the junction of the thalamencephalon with the prosencephalon. Immediately in front of the velum transversum, again, a median outgrowth of the prosencephalic roof grows upwards and backwards to form the "paraphysis" (*Par.*), discovered by Selenka in 1890. It was, of course, inevitable that the paraphysis should at first have been interpreted as the vestige of another "unpaired" sense-organ, but this view cannot be maintained. It never exhibits any trace of sensory structure, and is simply part of the same system of folds and outgrowths of the ependymal epithelium which gives rise to the velum transversum and to the choroid plexuses of this region. It may (*e.g.* in *Sphenodon*) become largely developed and assume the character of a follicular or tubular gland, which is probably concerned in the secretion of the cerebro-spinal fluid.

The two pineal outgrowths, the dorsal sac and the paraphysis, developed to varying extents in different types, have been the subjects of almost endless confusion in nomenclature, and in some cases (Lacertilia) they all seem to have been included together under the term "epiphysis" by the older writers. Their true relationships, as indicated by recent investigations, are shown in a diagrammatic manner in fig. 1.

Having thus briefly surveyed the general topographical relations of the pineal organs, we may pass on to consider the condition in which these organs are actually present at the present day and the manner in which they are developed in the different vertebrate groups. We shall find that the cases in which they still exhibit the structure of light-perceiving organs are comparatively few and distributed in an extra-

ordinarily sporadic manner, being confined to the Petromyzontidæ amongst cyclostomes, and the Rhynchocephala and Lacertilia amongst reptiles. In the myxinoids, the true fishes, the Amphibia, the Crocodilia, the Ophidia, the Chelonia, the birds and the mammals we can no longer recognise them as special organs of sense, even if they be present at all.[1] We shall find, further, that either one or the other of the original pineal outgrowths assumes dominance over its fellow and becomes much more highly developed, while at the same time it acquires a median position; or possibly in some cases the two have united together to form a median structure, of whose bilateral origin no trace remains, at any rate in the adult.

Amongst the Petromyzontidæ the pineal organs have been investigated in the European lampreys of the genus *Petromyzon* by Ahlborn (1883), Beard (1888), Owsjannikow (1889), Gaskell (1890), Studnička (1893 and 1899), Retzius (1895) and Leydig (1896), while to Kupffer (1894) we owe the most detailed account of their development. Johnston (1902) has given us some observations as to the corresponding organs in the American *Lampetra*, and the present writer has lately (1907) published a full account of them in the New Zealand *Geotria* (fig. 2), upon which the following description is mainly based. In all these cases there is a striking agreement in structure and relationships of the parts under discussion. There are two pineal organs, an anterior (*L.P.E.*) and a posterior (*R.P.E.*). The latter is always much more highly differentiated than the former, and actually lies in the middle line. In *Petromyzon* it lies on top of the anterior organ, but it is a significant fact that in *Geotria* the anterior organ lies in front of and a little to the left of the posterior. The posterior pineal organ is developed as a hollow outgrowth of the brain-roof, immediately in front of the posterior commissure (*C.P.*). It grows forwards above the roof of the brain, and its distal extremity enlarges to form the "pineal eye." The originally hollow stalk of the outgrowth solidifies, and nerve-fibres (*P.N.*) appear in it which connect the

[1] If we may believe the evidence afforded by the presence or absence of a parietal foramen, the sporadic character of the distribution of the "pineal eye" seems to have been no less pronounced in past geological epochs, for while in existing Rhynchocephala (*Sphenodon*) it is very well developed, in the closely related *Hyperodapedon* and *Rhynchosaurus* of palæozoic or early mesozoic age no trace of a parietal foramen exists, as I am informed by Dr. Smith Woodward.

"eye" with the brain. Some, at any rate, of these fibres pass to the right habenular ganglion (*G.H.R.*), others may be connected with the posterior commissure, and possibly with Reissner's fibre. The histological structure of the pineal eye is highly remarkable. It consists of a hollow, somewhat flattened vesicle, whose upper wall, the "pellucida" (*Pell.*), is composed of long columnar cells free from pigment, while the lower wall forms the so-called "retina" (*Ret.*), backed by a

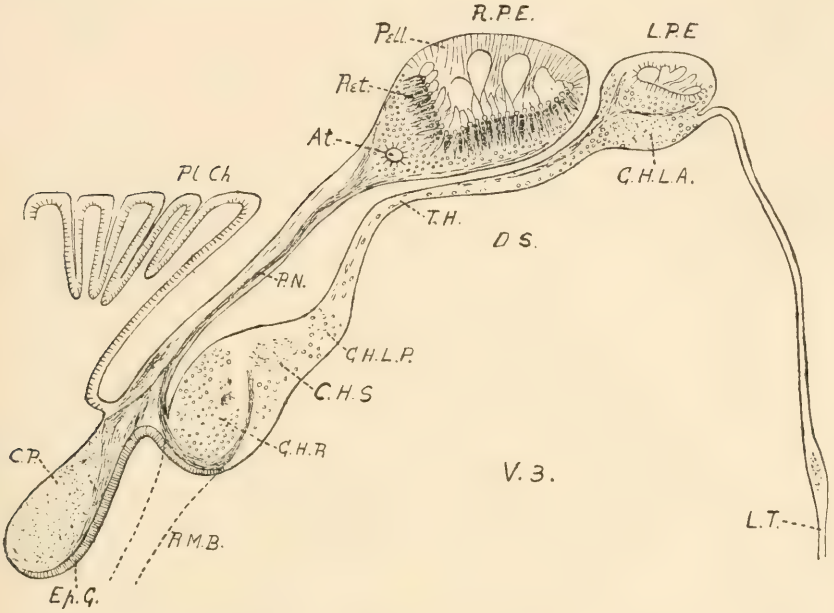

FIG. 2.—Diagrammatic sagittal section through the pineal organs and adjacent parts of the brain in a lamprey (*Geotria*).

At., "Atrium" of right pineal organ; *C.H.S.*, superior (habenular) commissure; *C.P.*, posterior commissure; *D.S.*, dorsal sac; *Ep.G.*, epithelium of ependymal groove; *G.H.L.A.*, anterior division of left habenular ganglion; *G.H.L.P.*, posterior division of same; *G.H.R.*, right habenular ganglion; *L.P.E.*, left (anterior) pineal organ; *L.T.*, lamina terminalis; *Pell.*, pellucida of pineal eye; *Pl. Ch.*, choroid plexus of mid-brain; *P.N.*, pineal nerve, lying in remains of pineal stalk; *Ret.*, retina of pineal eye; *R.M.B.*, direction of right Meynert's bundle; *R.P.E.*, right (posterior) pineal organ (pineal eye); *T.H.*, middle division of left habenular ganglion (tractus habenularis); *V.* 3, third ventricle.

thick layer of ganglion-cells and nerve-fibres. The retina contains sense-cells and pigment-cells. The former are long slender rods, with knob-like extremities projecting into the lumen of the vesicle and connected by delicate threads with the inner surface of the pellucida. The latter are columnar cells filled with minute granules of a glistening white material,

probably phosphate of lime, which constitutes the now well-known "white pigment" so characteristic of the pineal eye in the lampreys. There is no lens in the eye, and it seems quite impossible that any image should be formed upon the retina. The eye, however, lies immediately beneath a remarkably modified transparent area of the integument, so that it can be actually seen through the skin in the living animal (at any rate in *P. fluviatilis*), and this fact, taken in connection with its complex histological structure and its well-developed nervous connection with the brain, indicates that it may still function as a light-percipient organ. Experimental evidence is needed, however, before this point can be satisfactorily determined.

The anterior pineal organ (*L.P.E.*) is much smaller and forms a kind of very imperfect copy of its fellow; its lower wall contains little or no pigment and no fully developed sense-cells. It is connected with the left habenular ganglion, upon the anterior extremity of which (*G.H.L.A.*), indeed, it lies, and arises as a hollow outgrowth of the brain immediately in front of the superior commissure (*C.H.S.*) by which the two habenular ganglia are connected (Kupffer).

In spite of the fact that the two pineal organs in the lampreys actually arise one behind the other in development and maintain these relative positions throughout life, there are very strong grounds for believing that they are really members of a pair, of which the right one (pineal eye, upper epiphysial vesicle, posterior pineal outgrowth) is very much better developed than the left (parapineal organ, lower epiphysial vesicle, anterior pineal outgrowth). The evidence consists chiefly in the very remarkable asymmetry of the parts of the brain with which they are respectively connected. Thus the right habenular ganglion is very much larger than the left one, and so also is the right bundle of Meynert (*R.M.B.*). Now the ganglia in question are undoubtedly paired organs,[1] so also are the bundles of Meynert connected with them, and their extraordinary asymmetry can only be explained as the result of the unequal development of the sense-organs associated with them. It is, therefore, only reasonable to suppose that these sense-organs must themselves have originally been bilaterally arranged

[1] Although, owing to the hypertrophy of the right ganglion and the forward prolongation of the left one, they may appear one in front of the other in such a section as is represented in fig. 2.

structures, a conclusion which, as already pointed out, receives some additional support from the slightly left-sided position of the anterior pineal organ in *Geotria*. We shall see presently that the left-sided position of the anterior pineal organ is found also in bony fishes and in the tuatara (*Sphenodon*) (fig. 3).

The myxinoid cyclostomes afford a startling contrast to the lampreys in that no trace of pineal organs has yet been discovered in them. It is true that statements have been made to the contrary effect, but these are now entirely discredited, and the structure of the brain, differing as it does in such an extraordinary manner from that of the lampreys, renders it highly improbable that such organs exist.

In the true fishes the pineal organ, supposed to be homologous with the right or posterior pineal sense-organ of the lampreys, never exhibits any eye-like structure at all. In the adult elasmobranchs (e.g. *Spinax*) we find a median unpaired body in the form of a long, slender tube, which, arising from the brain-roof between the posterior and superior commissures, passes forwards above the brain and ends in a terminal enlargement lodged in a cavity in the cartilaginous roof of the cranium. Histologically the walls of this pineal organ exhibit a very uniform structure throughout its entire length, the most noteworthy feature being the presence of numerous modified ependymal cells, of columnar form, whose free extremities project slightly into the lumen of the organ (Studnička). Such cells are extremely characteristic of the pineal organ throughout the vertebrate series, and they have been compared to the sense-cells in the "retina" of those forms in which an eye-like structure is developed, but whether they themselves have any sensory function must be regarded as very doubtful. According to Studnička the organ is innervated by a bundle of nerve-fibres which comes from the neighbourhood of the posterior commissure, while it is not certain whether nerve-fibres also connect it with the habenular commissure, as has been observed in *Acipenser*. In the ganoids (e.g. *Acipenser*) the pineal organ is very similar in form and structure to that of elasmobranchs. In teleosts also we find the pineal organ composed of a "stalk" and a "terminal vesicle," the former being connected with the brain-roof exactly as in elasmobranchs, but remaining much shorter, while the terminal vesicle is usually larger, and may have its

wall much folded. According to C. Hill the wall of the vesicle in *Salmo* contains numerous cells resembling ganglion cells, and is connected with the posterior commissure by nerve-fibres, while in more than one genus Studnička has demonstrated the existence of the usual modified ependymal cells, with projecting, knob-like extremities.

Whilst almost invariably without any trace of its paired origin in the adult condition, the pineal organ of the true fishes may exhibit in its development strong evidence of an original bilateral symmetry. This evidence is most satisfactory in the case of certain teleost genera and in the ganoid genus

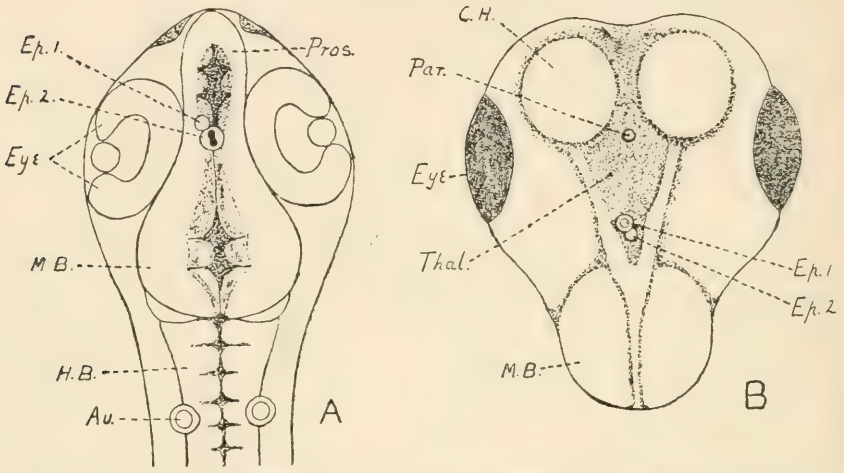

FIG. 3.—A. Head of embryo of a bony fish (*Coregonus*), showing the pineal outgrowths (after C. Hill). B. Head of embryo of tuatara (*Sphenodon*), showing the pineal outgrowths, etc. (after Dendy).

Au., auditory vesicle; *C.H.*, cerebral hemisphere; *Ep.* 1, anterior (left) pineal or epiphysial outgrowth; *Ep.* 2, posterior (right) pineal or epiphysial outgrowth; *H.B.*, hind brain; *M.B.*, mid-brain; *Par.*, paraphysis; *Pros.*, prosencephalon; *Thal.*, thalamencephalon.

Amia, investigated by C. Hill (1891 and 1894), who showed quite conclusively, in the first instance in the genus *Coregonus* (fig. 3, A), and afterwards in other forms, that the embryo possesses a right and left pineal vesicle, originating as paired outgrowths from the roof of the thalamencephalon, of which the right one gives rise to the adult pineal organ, while the left is vestigial. As in lampreys, however, the left vesicle (*Ep.* 1) may be placed somewhat more anteriorly than the right one (*Ep.* 2), so that it is possible to distinguish them as anterior and posterior pineal outgrowths respectively.

The work of Locy on the elasmobranch genus *Acanthias* is perhaps not so convincing as that of Hill on the teleosts and *Amia*, and requires confirmation. If his conclusions are correct we can recognise on the yet unclosed neural plate two pairs of symmetrically developed "accessory optic vesicles" behind the ordinary optic vesicles, with which they would appear to be serially homologous, and the pineal organ is said to be derived from the first pair. Other observers, however, describe the first appearance of the pineal organ in elasmobranchs as a median unpaired outgrowth, but it is not impossible that this may be preceded by the condition described by Locy.

The existence of a conspicuous parietal foramen in *Dolichosoma*, *Melanerpeton* and other extinct labyrinthodont genera has long been regarded as indicating the possession by these forms of a well-developed pineal sense-organ, but in all living Amphibia the parietal foramen has disappeared and the pineal organ has lost its eye-like character. In living Urodela and Apoda only a single pineal organ occurs, at any rate in the adult, and even this remains in a vestigial condition, apparently representing the proximal portion of the stalk of a more fully developed pineal organ such as occurs in fishes. It has the form of a small sac lying close upon the roof of the thalamencephalon and is less developed than in almost any other vertebrate group. In the Anura, on the other hand, the single pineal organ of the adult is differentiated into a proximal, sac-like "epiphysis," comparable to the remnant of the organ in Urodela and Apoda, and a distal vesicular "Stirndrüse," which lies altogether outside the cranium, and becomes more or less completely separated from the proximal portion by the closure of the cranial roof between them. The "Stirndrüse" is an almost spherical sac with cellular walls, of which the lower is much thicker than the upper. It is probably an extremely degenerate pineal sense-organ, and, as in the case of the corresponding organs in the lamprey, its position is indicated externally (in the common frog) by a "Scheitelfleck," clearly visible in the living animal as a small unpigmented spot lying on the top of the head between the paired eyes. Here again it is stated that a bundle of nerve-fibres runs from the dorsal commissure through the dorsal or posterior wall of the proximal portion of the pineal organ ("epiphysis"), which latter contains

the usual modified ependymal cells with free extremities projecting into its cavity.

Our knowledge of the development of the pineal organ in Amphibia is not in a very satisfactory condition, but Cameron in 1903 brought forward a certain amount of evidence to show that in frogs, toads and newts it has a paired origin. This author maintains that in the cases investigated by him the epiphysis or pineal gland arises in the form of two outgrowths from the roof of the thalamencephalon, one on either side of the middle line. The outgrowth on the right side disappears very early, while that on the left gives rise to the adult epiphysis. This is hardly what we should have expected, being exactly the opposite to what takes place in bony fishes. It is of course possible that the Amphibia, like the tuatara, differ from fishes in this respect, but confirmation of Cameron's results is much to be desired.

Turning now to the Reptilia, we find, as already stated, that amongst existing forms there are only two groups—the Lacertilia and Rhynchocephala—in which a "pineal eye" is still recognisable, although, just as in the case of the Amphibia, we find clear evidence in the parietal foramen of many extinct forms (e.g. *Ichthyosaurus*) that this organ was formerly more widely distributed in the group, and probably of much greater importance than it is at the present day.

It was, as we have already seen, in certain members of the group Lacertilia, viz. *Anguis* and *Lacerta*, that Leydig in 1872 first discovered the existence of a pineal sense organ. It was in *Anguis* also that De Graaf in 1886 first clearly demonstrated the eye-like structure of the organ in question, showing that it consists of a hollow vesicle whose wall is differentiated into a "retina" and a "lens," and which he regarded as the terminal portion of the "epiphysis" constricted off from the remainder.

The well-known researches of Baldwin Spencer in 1886 greatly extended our knowledge of the "pineal eye" in this group and supplied us with details as to its structure in many genera and species. This author showed that the organ varies greatly in different forms, apparently according to the degree of degeneration which it has undergone. Thus, while in such forms as *Anguis*, *Lacerta*, and *Varanus* the eye-like structure is still strongly in evidence, in *Chamæleo* it is reduced to a simple vesicle, ciliated internally, and with no trace of

differentiation into lens and retina, and in *Cyclodus* degeneration appears to have progressed until the "pineal eye" has either disappeared altogether or perhaps never becomes separated from the remainder of the "epiphysis."

Spencer, as is well known, regarded the "epiphysis" of the higher chordates as the homologue of the unpaired eye of the larval tunicate, and the "pineal eye" as a secondary differentiation of the distal part of the "epiphysis," with which it may remain connected by an optic nerve formed by a constricted portion of the latter.

According to more recent investigations—namely, those of Strahl and Martin and Béranek—the nerve of the "pineal eye" really arises quite independently of the "epiphysis," and is connected with the roof of the thalamencephalon in front of the latter and in the neighbourhood of the habenular commissure. De Klinckowström in 1893 also described the nerve of the "pineal eye" in embryos of *Iguana*, and traced it to the *right* habenular ganglion—a very remarkable result. According to him there is sometimes another nerve also which joins the "pineal eye" with the left habenular ganglion, and in one case he found yet a third nerve joining the "epiphysis" or "stalk" to the posterior commissure. In the adult, he tells us, the eye shows the variation characteristic of vestigial organs, and the nerve degenerates. It is obvious that further investigations on the nerve supply of the organs in question are much to be desired.

The development of the pineal organs in the Lacertilia is extremely interesting. All observers are agreed that at a very early stage two pineal organs appear on the roof of the thalamencephalon, just in front of the posterior commissure, very much as in fishes, and that one of these, situated in this case more anteriorly, develops into the pineal or parietal "eye," while the other becomes the so-called "stalk" or "posterior epiphysis" (see fig. 1). There is much difference of opinion, however, as to the exact relationships which these two structures bear to one another and to the brain. According to Leydig, for example, they are independent outgrowths of the brain-roof arising one behind the other, and this author also maintains that accessory parietal organs may be developed (*e.g.* in *Anguis*). According to another school, of which de Klinckowström may be taken as representative, the two organs arise one behind the other but the anterior is really an outgrowth of the

posterior, so that the pineal or parietal "eye," developed from the former, may perhaps after all be regarded as a portion of the epiphysis constricted off from the remainder, which forms the "stalk." This author also states that in *Iguana* the "stalk," after giving off the "parietal eye," may, by constriction of its apex, give rise to a second pigmented vesicle, which he distinguishes as the "Zirbel-Auge."

Some light is thrown upon this difficult problem by the investigation of the pineal organs and their development in the remarkable reptile *Sphenodon* (*Hatteria*), the sole surviving

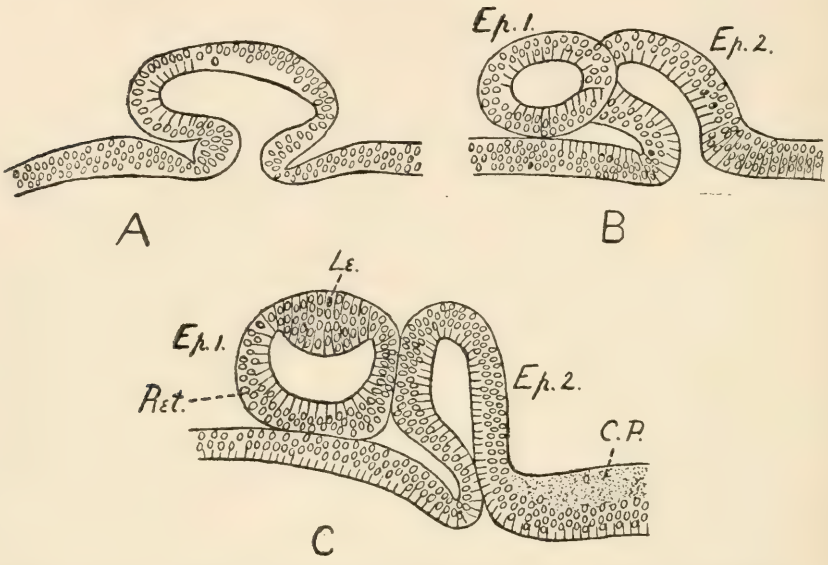

FIG. 4.—A, B, C. Three stages in the development of the pineal organs of the tuatara (*Sphenodon*), as seen in longitudinal vertical sections of young embryos. (The anterior end is towards the left side of the diagram in each case.)

C.P., Posterior commissure; *Ep.* 1, anterior (left) epiphysial outgrowth (pineal eye); *Ep.* 2, posterior epiphysial outgrowth (pineal stalk); *Le.*, "lens" of pineal eye; *Ret.*, retina of pineal eye.

representative of the very ancient group Rhynchocephala, and now confined to certain small islands off the coast of New Zealand, where it is known under the native name of "tuatara." This investigation I was fortunately able to carry out myself while in New Zealand, and the results were published in *The Quarterly Journal of Microscopical Science* in 1899. The earliest indication of the pineal organs in *Sphenodon* is in the form of a small vesicular outgrowth of the roof of the

thalamencephalon, situated a little to the *left* side of the middle line (fig. 4, A). At the next stage (fig. 4, B) we find the usual two pineal organs as seen in embryo Lacertilia: one placed a little in front of the other, and the cavities of the two perhaps still communicating with one another, while the cavity of the posterior also communicates with that of the brain. It is important to notice, however, that the more anterior of the two does not lie entirely in front of the more posterior, but partially overlaps it *on the left side*, as shown in figs. 3 B and 4 B. I had arrived at this result, and actually sent my manuscript and drawings to England for publication, before I was aware that Charles Hill, in America, had obtained a precisely similar result in the case of bony fishes (compare A and B, fig. 3). I think the fact of these two results having been arrived at quite independently is of great importance in estimating their true value. In bony fishes, however, as we have already seen, it is the right pineal organ which persists in the adult; and though it never gives rise to an eye-like structure in this group, it is doubtless homologous with the right (posterior) pineal sense-organ of the lampreys. In *Sphenodon*, on the other hand, the left (anterior) pineal organ of the embryo becomes the remarkably well-developed "pineal eye" of the adult. It separates completely from its fellow, and its upper wall very soon becomes thickened and lens-like, while its lower wall becomes deeply pigmented and gives rise to the "retina" (fig. 4, C). Although at first distinctly on the left side, it soon becomes median in position, and at the same time becomes widely separated from the brain, occupying the well-developed parietal foramen in the roof of the skull. The other pineal outgrowth, or so-called "stalk" (*Ep.* 2), appears to occupy a median position from the first; nevertheless it probably represents the right-hand member of an original pair. Its development differs widely from that of its fellow. It becomes greatly elongated and finger-shaped, and curves forwards over the roof of the thalamencephalon towards the pineal eye, which lies a little in front of and above its apex. Its cavity for a long time continues in free communication with that of the brain at the point of origin, between the closely approximated superior and posterior commissures. The nerve of the pineal eye appears as a band of fibres running from the retina beneath this so-called "stalk"; but its connection with the brain-roof has unfortunately not yet been made out. From

these results we may conclude, with a considerable degree of probability, that the anterior and posterior pineal organs of the Lacertilia, as well as of the Rhynchocephala, represent the vestiges of an original pair of sense-organs.[1]

The structure of the "pineal eye" in the adult *Sphenodon* was first investigated by Baldwin Spencer in the memoir so often referred to already. Spencer showed that it exhibits an unusually high degree of histological differentiation; but the use of more recent methods of preparation has brought to light still further details of structure, and necessitated some modification of Spencer's views.

The organ has essentially the same structure and relations as in those Lacertilia in which it is still well developed, consisting of a hollow vesicle lying in the parietal foramen beneath a "parietal plug" of specially modified connective tissue. The upper wall of this vesicle is greatly thickened to form the so-called "lens," which is almost disconnected from the "retina." The retina consists of (1) slender rod-like cells, which lie next to the cavity of the vesicle with their inner extremities projecting freely into the latter for a short distance, while their outer ends are connected with slender nerve-fibres; these rods have conspicuous nuclei and are separated from one another by numerous minute pigment granules of a dark brown colour; the cells in which the pigment granules are developed have not yet been made out; (2) behind the rods lies a layer of nerve-cells and fibres, and (3) at the outer limit of the retina is a layer of cells which are probably supporting elements.

The nerve of the pineal eye is very well developed, even in the adult, and can easily be traced into continuity with the layer of nerve-cells and fibres behind the rods.

The "lens" is biconvex in form and also of complex histological structure. Its outer half is made up of nucleated columnar cells lying at right angles to the surface; the inner half is composed of somewhat similar cells which, however, appear to contain numerous delicate fibrillæ and bodies resembling centrosomes. The most remarkable feature, however, is the presence of a large central cell of irregular form, resembling a ganglion cell.

[1] It is possible that, as de Klinckowström suggests, the proximal portion of the "stalk" may be common to the two organs; in this case the apex of the stalk only would represent the right pineal sense-organ. The structure of this apex in *Sphenodon*, with its pigmented lower wall, tends to support this view.

The cavity of the optic vesicle contains a network of delicate fibres which are attached, on the one hand, to the projecting ends of the rods, and on the other to the inner face of the "lens."[1]

It appears, therefore, that in certain details of structure, as well as in its general form and relations, the pineal eye of *Sphenodon* closely agrees with that of the lampreys. Especially noteworthy are the projecting apices of the rods and their connection with the back of the "lens" by a network of fibres. There are also, of course, important differences, especially in the character of the retinal pigment, which is dark brown in *Sphenodon* and white in the lampreys, and in the structure of the upper wall of the vesicle, which in the lampreys is comparatively simple histologically and by no means lens-like in form. In the lampreys, indeed, as Studnička has pointed out, the pineal eye is not a "cameral eye" at all; whether or not it is so in *Sphenodon* and the Lacertilia may also be questioned. The structure of the "lens" in *Sphenodon* seems to indicate some other function than that of merely focussing light-rays; while the presence of pigment in the "lens" of *Varanus*, as demonstrated by Baldwin Spencer, would seem to render it useless as a lens. In the latter case, however, we may be dealing with modifications in structure consequent upon degeneration.

If we accept the principle that the degree of morphological and histological differentiation of an organ is an index of its functional activity, we cannot escape the conclusion that in *Sphenodon*, and also in *Petromyzon* and *Geotria*, the "pineal eye" is something a good deal more than a mere vestigial structure. Organs which have lost their function undergo reduction and simplification, as witness the ordinary eyes of many animals which habitually live in the dark (e.g. *Proteus*). No doubt this is the case with the pineal sense-organs of the vast majority of vertebrates, but in the case of the forms just mentioned we must, at any rate for the present, suspend our judgment.

It has frequently been pointed out that there is a great morphological difference between the "pineal eyes" and the ordinary paired eyes of vertebrates, inasmuch as the former

[1] The minute structure of the pineal eye in *Sphenodon* has as yet, so far as I am aware, been investigated in only a single properly fixed specimen, and further observations are needed in order to show how far the results obtained are of general occurrence.

are constructed upon the so-called "invertebrate type," with the optic nerve spreading out over the back of the retina, while the latter are constructed upon the "vertebrate type," in which the optic nerve pierces the retina and spreads out over its inner face. If we study the development of these organs, however, we shall find that there is really no very fundamental difference between them. Both originate as hollow outgrowths of the fore-brain; in both the actual sense-cells or "rods" are formed from the innermost layer of cells, next to the original cavity of the optic vesicle (in other words, they are modified ependymal cells), and in both the original optic stalk is replaced by nerve-fibres constituting the optic nerve. The apparent difference in the relation which the nerve bears to the retina is due simply to the invagination of the wall in the ordinary paired eye to form an optic cup, whereby the original cavity of the optic vesicle is obliterated, and a space which is really altogether outside the optic vesicle becomes enclosed as the posterior chamber of the eye. Thus it comes about that the portion of the original optic vesicle which becomes the "pellucida" in the pineal eye of the lamprey and the "lens" in that of the lizards and the tuatara, becomes invaginated and forms the retina in the ordinary paired eyes, while the part which forms the "retina" in the "pineal eyes" of both types forms merely the pigment epithelium at the back of the retina in the ordinary paired eye. The development of the paired eyes teaches us that some, at least, of the fibres of the optic nerve grow out from the front face of the retina (*i.e.* the morphological outer surface of the original optic vesicle) and over the lip of the optic cup at the choroid fissure, and thence to the brain along the optic stalk. It is thus evident that the primary relations of the optic nerve and the retina are precisely the same as in the "pineal eye." It is hardly necessary to point out that the lens of the paired eyes is an altogether new development not represented at all in the pineal eye.

There is, therefore, nothing in the structure or development of the "pineal" and "paired" eyes respectively to prevent us from regarding them, with Locy, as being serially homologous with one another.

In reptiles other than Rhynchocephala and Lacertilia, as already stated, the pineal organs no longer show any trace of eye-like structure. In view of the apparently close relationship of the Ophidia to the Lacertilia, we might have expected to

find in the former group at least some indication of a pineal sense-organ, even in the adult, but such is not the case. On the other hand, we find in the snakes a condition of the epiphysis somewhat resembling that which obtains in birds and mammals; the organ being represented by a highly vascular solid body, which may perhaps be regarded as a ductless gland. In the Crocodilia the degeneration of these organs appears to have been carried to its extreme length, and neither in the embryo nor in the adult can we recognise any trace of an epiphysis whatever.

In birds, again, all traces of the pineal sense-organs appear to have disappeared. The epiphysis in this group may be either tubular, follicular, or solid, and is usually connected with the brain by a hollow or solid stalk. It consists (in *Meleagris*) of a vast number of small follicles lined by ependymal epithelium and separated from one another by vascular connective tissue, and Studnička has demonstrated the presence of ependymal cells with extremities projecting into the cavities of the follicles. Here again we are probably dealing with a ductless gland which passes its secretions into the blood. The epiphysis in this group is generally stated to arise in the embryo as a single outgrowth of the roof of the thalamencephalon, but indications of a paired origin have been observed by several investigators, especially Cameron.

Lastly, amongst the Mammalia we find a condition very similar to that which obtains in birds—the epiphysis being represented by a presumably glandular organ, made up of a vast number of follicles separated from one another by vascular connective tissue, and lined by ependymal epithelium. Here, once more, we probably have before us a ductless gland of unknown function, formed most likely by the metamorphosis of the "stalk," or a portion of the "stalk," of one or both of a primitive pair of epiphysial outgrowths. A remarkable feature of this gland in the human subject is its function of secreting the so-called "brain-sand," consisting of concretions of carbonate and phosphate of lime and magnesia, but whether or not this secretion can be legitimately compared to the formation of the "white pigment" in the pineal eye of the lampreys, as has been suggested, must be regarded as extremely doubtful.

It would appear, therefore, that at the present day we actually know no more than did Descartes of the function of the pineal gland in the highest vertebrates. We know much, however, of

its wonderful history, as revealed by the study of comparative anatomy and embryology, and this knowledge confers upon it a much more legitimate and scientific, if less popular, interest than that which formerly attached to it as the supposed "seat of the soul." What we now want, more than anything else, in order to extend our knowledge in this direction, is a series of careful physiological investigations, by experimental methods, into the functions of the pineal organs, not only in those forms in which one of them still retains the structure of a sense-organ, but also in those in which such structure can no longer be recognised and the "epiphysis" appears to have undergone a complete change of function and assumed the character of a ductless gland.

THE SEQUENCE OF PLANT REMAINS IN THE BRITISH PEAT MOSSES

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Although peat deposits occur throughout Europe they attain their greatest extent and depth in the north-west of the Continent. Precise figures are not obtainable, but these deposits cover a considerable proportion of the whole of Germany, Denmark, Sweden, and the Jura range in Switzerland. The interest of such deposits lies in the fact that they consist wholly of the remains of plants which have existed over these areas during a long space of time. Further, when it is remembered that all the larger peat areas that have been examined show a definite stratification, and that the lower layers frequently contain the remains of an arctic vegetation in regions which now support a temperate flora, it will be seen that from a botanical and geological point of view it is important to make a systematic investigation of the successive strata over considerable areas. Such investigations might be expected to throw light upon the changes in distribution undergone by the British flora since its immigration from the Continent in post-glacial times, and also give direct palæontological evidence for a long period of time during which, geologists are agreed, many climatic changes have occurred, though the amplitude of such changes is still a matter of controversy. Differences in climatic conditions of comparatively small amplitude would certainly affect the character and distribution of vegetation to a greater degree than the alluvial drifts which were deposited whilst those changes were in progress.

The researches of Continental botanists and geologists during the last thirty years have shown that systematic investigation of peat deposits are capable of giving definite and unmistakable evidence upon these questions. Since 1870, when Nathorst (1) first described the occurrence of an arctic vegetation in fresh-water clays at the base of the peat mosses near Alnarp in

Sweden, an extensive literature dealing with this subject has grown up in Norway, Sweden, Denmark, Germany, and Switzerland. In Scandinavia particularly, the work of Nathorst, Gunnar Andersson, Wille, A. Blytt has made it possible to trace the path followed by the flora, as it immigrated during the shrinkage of the ice-sheet, to gain some idea of its gradual change in distribution during succeeding epochs and to reconstruct the climatic changes which occurred during post-glacial times.

The general sequence of the plant remains in the Swedish peat may be briefly described. At the base, the remains of an arctic flora have been found enclosed in fresh-water clays and silt. The flora consists of *Dryas octopetala*, *Salix polaris*, *S. herbacea*, *S. reticulata*, *S. arbuscula*, *Betula nana*, *Arctostaphylos alpina*, *Empetrum nigrum*, *Diapensia lapponica*, *Myrtillus uliginosa*, and other plants of a like arctic character. Owing to the abundance of Dryas remains, this zone is generally spoken of as the Dryas Zone. This flora had a wide distribution during late glacial times, as it has been discovered in Sweden, Norway, Denmark, Germany, and Russia. This basal arctic vegetation is overlaid by a considerable thickness of peat containing the remains of four forest-beds. The lowest, immediately overlying the Dryas Zone, was formed chiefly of birch (*Betula odorata*, *B. subalpina*, *B. tortuosa*), with aspen poplar (*Populus tremula*), juniper, and a few species of willow. The accompanying flora is subarctic rather than arctic. The birch zone is succeeded by three separate forest beds of pine (*Pinus sylvestris*), oak (*Quercus robur*), and spruce (*Picea excelsa*) respectively.

In the British Isles the present distribution of peat deposits shows a general tendency to follow the maximum rainfall, the deposits being comparatively scanty on the eastern side of England and Scotland, and increasing in area and thickness as the western coasts are approached—the greater development occurring in the Hebrides, the western part of the Scottish mainland, and in the west of Ireland. In the hill districts they reach their greatest development upon smooth, flat-topped hills, like the Pennine chain in England, the elevated plateaux of the Grampian mountains, and in elevated districts surrounded by mountains, such as the moor of Rannoch in the west of Scotland.

Yet if the peat in such districts is examined, it is found that there are traces everywhere showing that the present conditions

are not sufficiently moist to favour peat growth ; for the upland valley, hill-side, and hill-top peat, almost without exception, is in a state of rapid denudation, being traversed by channels and furrows often 12 or 15 ft. in depth. If the sides of these gullies are examined, the stems and roots of large trees are often seen exposed as the bank is gradually cut back by the stream at its base. Where the peat is deep and the stream has cut its way down to the soil, it becomes evident that the tree-roots and stems are arranged in a definite layer. Sometimes one, more frequently two, and occasionally three such forest beds can be recognised, separated by thick beds of peat quite free from any traces of trees. These forest remains are frequently present in the peat in districts where no trees will grow at the present day ; to take but two instances, forest remains are abundant in the peat of the now treeless Hebrides and Shetlands, and on the summits of the Grampians at more than 3,000 ft. above sea-level. The great thickness of many of our peat deposits (sometimes reaching 30—50 ft.), the known slow rate of growth of peat, and the general presence of two forest beds, is evidence that the conditions have changed considerably since the mosses began to form, and a closer examination has shown that large areas of peat in Britain date back to the later phases of the glacial period.

All the peat areas examined in Scotland lie some distance from crofts or villages, and the strata show no sign of having been disturbed by human agency. Sections are cut down through the successive strata until the underlying rock, gravel, or sand deposits are reached. Each section is made just large enough to work in conveniently. Over areas where the peat is of moderate depth, the sections are usually 8 or 9 ft. in length and 4 ft. wide. In some districts, such as the Shetlands, where the peat is frequently 18—19 ft. in depth, the sections have to be made 17—20 ft. in length, to allow a series of platforms to be left at each end, upon which the peat from near the base of the section can be placed. In some of the areas a good deal of difficulty is experienced in cutting through the Upper Forest of pine. The timber proves to be so large and tough, and so closely packed, that it is impossible to cut through it with a spade, and it is necessary to clear away the large trunks and roots of the pine with the aid of an axe and saw before the underlying peat can be excavated.

In the examination of the peat samples brought back to the laboratory, much help has been obtained by the use of the method described by Gunnar Andersson (2). Samples of the peat are treated with nitric acid, which completely deoxidises the material, loosens, and at the same time bleaches it. The peat is then placed in sieves and the loose débris washed away, leaving any seeds and fruits which it may contain. Fragile leaves are usually broken into fragments during this process, and they can best be obtained by dissecting them out from the peat without previous treatment.

In the south of Scotland two forest beds invariably make their appearance—a lower of birch (*Betula alba*) and an upper of pine (*Pinus sylvestris*). The Lower Forest rests directly upon glacial deposits and contains an assemblage of plants indicating climatic conditions not unlike those of the present day. This is overlaid by 3 or 4 ft. formed almost entirely from the remains of *Sphagnum* and *Eriophorum vaginatum*. Above this, the plant remains indicate an entirely different set of conditions, for peat bog plants are replaced by an assemblage of well-marked arctic plants, such as *Loiseleuria procumbens*, *Salix reticulata*, *S herbacea*, together with *Empetrum nigrum*. *Salix reticulata* now grows only on the summits of the higher Scottish mountains, generally above 3,000 ft., and its presence between two forest beds in the south of Scotland indicates a period when the valleys in the south of Scotland had a climate at least as rigorous as that at present obtaining on the summits of the highest Scottish mountains. If climatic conditions were such over the south of Scotland, it is extremely probable that glaciers would exist at the same time amongst mountainous ground in the Highlands.

The gradual dying away of this cold period and the incoming of a forest vegetation is faithfully reproduced in the peat. Arctic willows and creeping azalea give place above to beds of *Eriophorum* and *Sphagnum*. Later, the wet moorland conditions indicated by these plants yield to pine forest in most districts of the south of Scotland. This forest period at length came to an end and was succeeded by wet conditions, as the peat immediately above the forest zone is formed entirely from *Scirpus*, *Sphagnum*, and *Eriophorum*.

The Highland areas reproduce the later stages found in the Southern Upland peat, but the earlier stages are wanting. The basal layers contain the remains of an arctic flora similar to

that met with between the two forest beds in the south. Above this lies *Sphagnum* and *Eriophorum* peat covered with the Upper Forest and recent peat. The Upper Forest consists of two distinct zones separated by 1—3 ft. of *Sphagnum* and *Scirpus* peat quite free from traces of wood. This is a feature of constant occurrence in the Highlands, but has not been found in the south of Scotland.

As about twenty-four districts have been investigated during the last three years between the south of Scotland and the Shetland Islands, Aberdeenshire and the Outer Hebrides (3), the geographical distribution of the principal zones and the variations shown by the same horizon in different districts may be briefly indicated.

The following stages are represented in the peat of the south of Scotland, the Highlands, and the Hebrides:

1. Recent peat.
2. Forest.
3. Peat bog plants with arctic plants.
4. Forest.
5. Peat bog plants.
6. Arctic plant bed.
7. Peat bog plants.
8. Forest.
9. Arctic plant bed.

It is obvious that some terminology must be used in discussing the distribution of these beds, and it will be simpler to provisionally name them for the purpose of description and then point out the possible correlation of the strata with stages in the glacial period for which a terminology already exists.

The following names will then be adopted:

1. Recent peat.	
2. Forest bed.	Upper Forestian.
3. Peat bog plants with Arctic plants.	
4. Forest bed.	
5. Peat bog plants.	Upper peat bog.
6. Arctic plant bed.	Second arctic bed.
7. Peat bog plants.	Lower peat bog.
8. Forest bed.	Lower Forestian.
9. Arctic plant bed.	First arctic bed.

Strata 2, 3, 4, are all classified as "Upper Forestian" for reasons which will be given later.

The First Arctic Bed.—This bed has so far only been met in the Outer Hebrides and the Shetland Islands. Occurring at the base of all the beds and resting upon the glacial deposits it represents the arctic flora covering the peat areas before the growth of the overlying temperate Lower Forest. The flora is best preserved in Shetland, where the remains of *Salix reticulata*, *S. herbacea* × *Lapponum*, *Betula nana* form a layer of closely compressed peat about 1 ft. in thickness.

Such creeping Salices occur on the summits of many of the Highland mountains above 2,000 ft. at the present time; but the conditions in Shetland must then have been entirely different to those which now obtain on our mountain summits, for below the bed of creeping willow occur many aquatic plants such as *Carex ampullacea*, *Menyanthes trifoliata*, *Ranunculus repens*, *Equisetum* sps., *Viola palustris*, *Potamogeton pectinatus.* These plants do not occur on the dry wind-swept summits where arctic willows now grow in Britain; the flora rather suggests an arctic marsh or tundra with many scattered pools containing an aquatic vegetation.

This bed, so frequently underlying the arctic willow, can hardly belong to an earlier stage in the peat history, as the leaves of *Salix reticulata* are frequently present amongst the aquatic and marsh plants, and have evidently been blown in from the surrounding moorland. The aquatic zone contains much silt, clay, and sand, whilst the bed of creeping willow is entirely free from any such deposits.

After the ice retreated the ground must have been intersected by numerous rills, streams, and pools in which grew *Equisetum*, *Potamogeton*, and *Menyanthes.* Muddy streams frequently covered this vegetation with fine silt and sand. The drier ground was covered with a close growth of *Salix reticulata* and other arctic-alpine plants, which, as the pools gradually became silted up, spread over these spots also. It is quite evident that the climate of that period allowed a fairly lengthy time for the flowering and ripening of the seeds of these aquatic plants. In fact, the flora indicates a wet, cold climate, rather than dry conditions with an arctic temperature. Either the first arctic bed began to form some time after the disappearance of glacial conditions or the rise of temperature must have been very rapid during the wane of the glaciers. The richness of the flora indicates that the glacial stage,

represented by this bed, was much later than the main ice-sheet.

In a recent account of the development of the Scandinavian flora, Gunnar Andersson (4) records the occurrence of *Potamogeton filiformis*, *P. prælongus*, *Menyanthes trifoliata*, *Batrachium confervoides*, and other aquatic plants in the Dryas Zone, and infers that the Scandinavian climate of that time was not arctic like that, for instance, of North Greenland, but rather resembled South Greenland at the present time. This conclusion is in complete agreement with the features found in the north-west Highlands. Each arctic stage appears to mark a period of great precipitation, and these apparently alternated with comparatively dry temperate stages. The character of the first arctic bed is different in the Outer Hebrides—the only other district in which the peat is old enough to go back to this date. In Lewis, the older layers contain *Salix arbuscula*, *Betula nana*, *Potentilla Comarum*, *Empetrum nigrum*, *Menyanthes trifoliata*, *Potamogeton* sp.

Some of these are plants of wide distribution from temperate to arctic regions: others like *Betula nana* and *Salix arbuscula* have an entirely arctic or sub-arctic distribution, and do not now occur near sea-level in Britain; but these basal beds suggest less rigorous conditions than those in the Shetlands, for bog plants of wide distribution are the most abundant, whilst in the Shetlands *Salix reticulata* is the characteristic plant.

The plants of the first arctic bed must have immigrated to Scotland either across the North Sea or through England. The incoming flora would probably pass along the higher ground while the valleys and lowlands were still covered with the shrinking remnants of the local ice-sheets. The evidence from the mosses in Lewis certainly suggests that the incoming arctic flora barely established itself in the extreme west of Scotland before the Lower Forest overspread the peat bogs, as the typical arctic plants represented in Shetland are either absent or poorly represented in the corresponding zone of the Hebrides.

The Lower Forestian.—Considerable interest attaches to the flora of this zone, owing to the absence of any arctic or sub-arctic plants, suggesting that a complete change of conditions took place between the first and second beds, during which the arctic flora withdrew from the peat areas.

In the Southern Uplands, Hebrides, and the Shetlands the Lower Forest is well preserved, the trees being *Betula alba*, *Corylus avellana*, *Alnus glutinosa*. The list of accompanying plants is not large, as the peat is chiefly formed of wood débris and bark. Inferences as to temperature drawn from these trees alone are inconclusive, but certain features presented by the distribution of the forest bed bear directly upon the general climatic conditions of that time. The presence of a buried forest extending to the western coast of Shetland points indubitably to the fact that the path of the Atlantic cyclonic systems must then have been different from that of the present day. Trees are now entirely absent from Shetland, although many attempts have been made to form plantations in sheltered spots. Planted in gardens, ash, rowan, and birch grow as high as the surrounding walls, and are then stunted by the winds, so that the trees appear to be shorn off at the level of the protecting wall. If this takes place at the inland and more sheltered spots, it is still more difficult to account for the presence of the buried forest near the cliffs of the west coast, where the full force of the Atlantic gales is felt, as they succeed one another during the greater part of the year. As the mean annual temperature of the Shetlands is perhaps higher than many parts of Britain which are tree-clad, the absence of trees in these islands must be due, not to temperature, but to the force of the salt-laden winds.

The accompanying flora of the Lower Forest contains many plants of wide distribution which do not give any definite evidence with regard to temperature. The zone also contains other plants which are not usually found accompanying arctic plant associations, such as *Ajuga reptans*, *Ranunculus lingua*, *Lychnis diurna*, *Salix purpurea*.

But the most significant fact is that none of the characteristic arctic plants of the first and second arctic beds are to be found in the Lower Forest bed, though quantities of material from the south of Scotland, the Hebrides, and the Shetlands have been worked through. If it still be urged that there is no direct proof that the Lower Forest bed was accumulated under temperate conditions, one may ask what was the reason for the disappearance of the characteristic plants of the first arctic bed during this period, and why should these typical

arctic species again appear as the strata above the Lower Forest are reached?

The upward limit of tree growth has been used both in Britain and on the Continent as the approximate boundary between the sub-alpine and alpine floras, and it is found that a considerable difference in altitude separates the zone of natural woodland from the alpine associations.

From this, the first arctic bed appears to be the result of the depression of the present alpine-arctic boundary in Britain to the extent of about 2,000 ft., whilst the Lower Forest zone represents the return of that boundary to at least its present altitude.

The absence of these two beds from the Highland districts is remarkable. Either conditions were not favourable for peat formation in those areas during the first arctic, the Lower Forestian, and the lower peat bog period, or peat formed during those periods was subsequently removed either by glaciation or by atmospheric agencies. Further areas must be examined before it is possible to say which view is correct.

At the same time it must not be forgotten that water action frequently plays a great part in the removal of peat beds. Many cases have come under notice in various parts of Scotland and the north of England where the older beds along a stream-side have been swept away and replaced by mounds of sand and gravel. One example is found at a sharp bend in the Abhuinn-a-Coire-Bhuig in Eastern Ross, where all the older peat beds have been washed away and replaced with sand and gravel. This event occurred before the Upper Forestian and most probably during the upper peat bog stage. It is not of course suggested that the absence of the older peat beds throughout the Highlands can be due to water action of this character, but the example is given in order to emphasise the many occurrences which may be responsible for the absence of the older beds of peat in some districts. It is quite evident that peat formation is dependent upon many factors such as temperature, humidity of climate, drainage, character of soil, and the flora, or the peat deposits of Britain would not be so local in distribution.

No trace of *Pinus sylvestris* has been found in the Lower Forest, although it is the most characteristic tree of the Upper Forest. If native in Scotland at that time, it is difficult to see

why it should not occasionally have spread over the peat-covered areas, but neither in the south of Scotland nor in the Hebrides and Shetlands is any trace of it to be found.

The Lower Peat Bog.—This zone is present in the low-lying Wigtownshire mosses, and the other areas examined in the Southern Uplands, in Skye, the Outer Hebrides, and in the Shetlands. In the Southern Upland areas and the Shetlands it exhibits the greatest uniformity, the bulk of the peat being formed from the remains of *Sphagnum*, *Scirpus cæspitosus*, *Eriophorum vaginatum*, *Molinia cærulea*, Carices, *E. angustifolium*. *Calluna* is scarce or absent, and the peat areas at this time seem to have formed extremely wet *Scirpus* and *Sphagnum* moors, and trees appear to have been entirely absent. The peat bears every sign of having been formed under conditions eminently favourable for peat growth, and although this zone frequently attains a thickness of 5—7 ft., it is probable that it was formed in less time than the first arctic bed, which is only 18 in. in average thickness.

In the low-lying mosses of Wigtownshire, Skye, and North Uist a different type of flora overspread the peat during this stage, for the lower peat bog there consists of the remains of *Phragmites communis*, *Equisetum* sps., *Menyanthes trifoliata*. In fact, these areas must have been covered with a series of shallow lakes and swamps, possibly explained by the fact that the peat rests upon stiff clays, whilst many of the Southern Upland mosses rest upon sands and gravels. In Lewis, the lower peat bog approximates more to the Southern Upland type, being composed of *Sphagnum*, *Eriophorum angustifolium*, *Erica tetralix*.

A noticeable feature is the fact that the lower peat bog tends to thin out as it is traced across Scotland from the south to the north. This is a phenomenon of some interest, particularly when considered in connection with the significance of the succession of the peat strata. It is evident that these successive beds represent changes in plant distribution on a great scale and occupying presumably considerable spaces of time.

The lower peat bog stage undoubtedly represents a great invasion of North Britain by swamp and bog plants which previously had their centre either in the south or east of Britain. If that be so, the arrival of this type of flora would

be much later in the extreme north of Scotland than, for instance, in the Southern Uplands. It is perhaps not without significance that in Shetland the lower peat bog thins out to a bed only a few inches in thickness or a layer of diatomaceous earth. The centre of distribution of these swamp and bog associations could hardly have been in the north of Britain during the growth of the Lower Forest, and the farther the areas were from this centre the longer it would be before they were colonised.

The Second Arctic Bed.—The lower peat bog is succeeded by a flora composed mainly of typical arctic plants, and is represented in every district so far examined from the Southern Uplands to the Shetlands.

In the south of Scotland the zone contains *Salix reticulata*, *S. herbacea*, *Loiseleuria procumbens*, *Empetrum nigrum*, *Arctostaphylos alpina*, but in the Shetlands, *Salix reticulata*, *Betula nana*, *Empetrum nigrum*, *Salix arbuscula*, *Erica tetralix*. In these areas the second arctic bed occurs between the lower and the upper peat bog, but in the areas which lie within the Highlands no older beds lie below this zone and it rests directly upon sands, gravels, and clays. In such districts the bed is thicker and contains a richer flora than in the Shetlands and south of Scotland. In the areas stretching from the Grampian mountains to Cape Wrath the peat of this bed contains *Dryas octopetala*, *Salix reticulata*, *S. herbacea*, *Arctostaphylos alpina*, *Betula nana*, *Veronica alpina*, *Lychnis alpina*, *Salix arbuscula*, *Carex* sps., *Equisetum* sps., *Empetrum nigrum*, *Potentilla Comarum*, *Viola palustris*, *Menyanthes trifoliata*.

In the district near Cape Wrath these arctic plants are frequently underlaid by a thin seam of peat a few inches in thickness, composed of the remains of aquatic or marsh vegetation consisting of *Ranunculus repens*, *Potamogeton* sps., *Menyanthes trifoliata*. This seam is not continuous, but appears to underlie the *Salix* beds in small patches and frequently in depressions of the ground, and marks the position of small swampy patches during the second arctic period.

In districts lying in the extreme west, such as Skye, North Uist, and Lewis, the second arctic bed is not recognisable, and the first arctic bed is but poorly represented. In fact, the two successive waves of arctic vegetation do not seem to have pene-

trated to these outlying islands. After the close of the Lower Forestian the general type of vegetation over these peat mosses seems to have remained very uniform through the lower peat bog, second arctic stage, and the Upper Forestian to the present day. During those periods the mosses in the Hebrides must have resembled the tundra of Northern Siberia described by Sewell (5). The observations from the Shetlands illustrate the same feature, for although the second arctic bed is present, yet the Upper Forest does not seem to have spread over the peat areas. Shortly stated, the farther one passes to the edge of the continental plateau the more uniform does the flora appear to have remained, since the later stages of the glacial period. This may imply either that the climatic conditions have been more uniform in those regions, or that the successive waves of vegetation passing over the mainland did not penetrate there on account of natural barriers to immigration. The peat does not afford any direct evidence upon these points, for whilst the second arctic bed was being formed on the mainland, the peat mosses of the Hebrides were covered with marsh consisting of *Phragmites communis* and *Equisetum*, which might well occur under sub-arctic or under temperate conditions.

The Upper Peat Bog is developed in all districts, and the flora is generally very similar to that of the lower peat bog. In some of the Highland areas, such as the Spey-Findhorn watershed, Findhorn-Nairn watershed, Coire Bog, Cape Wrath district, Rannoch Muir, remains of small *Betula alba* shrubs occur in the lower parts of this zone. The wood is very local in occurrence, whilst the main mass of the peat is formed of *Scirpus cæspitosus*, *Eriophorum angustifolium*, *E. vaginatum*, and *Sphagnum*. Evidently these small clumps of shrubby birch were soon displaced, as no wood is met with above the first plot or so of the upper peat bog. In the Hebrides and the lowland mosses of Wigtownshire the upper peat bog is simply a continuation of the lower peat bog, there being no layer of arctic plants between.

The Upper Forest Bed.—This zone is confined to the mainland of Scotland, from the lowland mosses of Wigtownshire to the valley of the Dionard south of the Kyle of Durness, near Cape Wrath. Whilst the flora exhibits remarkable uniformity, some interesting and important modifications appear as the bed is traced northwards through Scotland. In the areas of the south

of Scotland the forest consists of *Pinus sylvestris*, with the exception of some parts of Tweedsmuir, where *Betula alba* replaces pine. As soon as the Highland areas are entered the Upper Forest divides into two distinct zones separated by 1—3 ft. of peat in which no wood is found. In the Spey-Findhorn, Findhorn-Nairn, and Coire Bog districts the peat between the upper and lower layers of this forest is formed from *Sphagnum*, but in areas examined in the Grampians, and in Assynt, *Betula nana* and *Salix arbuscula* are abundant between the two layers of forest remains. The presence of these plants in some districts and of *Sphagnum* beds in others, between two layers of well-developed pine forest, is significant, and points to a decided break in forest conditions at this time. This phenomenon is too widespread to be due to local causes, for it is a constant feature in all the Highland areas examined.

Betula alba replaces *Pinus sylvestris* in the lower zone of the Upper Forest on the Grampians, in Assynt, and over much of the Caithness-Sutherland border—in other words, at high elevations and in the extreme north. It is remarkable that until the Upper Forest is reached no extensive beds of *Calluna* are found. The Vaccinium-Calluna association, now so constant a feature on moorlands in Scotland and England, appears to be a comparatively recent feature.

The Peat above the Upper Forest.—The peat of varying thickness lying above the Upper Forest presents the same features as the lower and upper peat bog. Occasional beds of *Calluna* or *Eriophorum* make their appearance, but are not continuous over large areas, and are evidently due to local causes. The general flora is of a distinctly wetter type than that characteristic of many of the peat areas of the present time, as it consists mainly of *Scirpus cæspitosus* and *Sphagnum*.

During the last thirty years much work has been done in Britain by various investigators upon plant remains in Pleistocene beds, and such work is admirably summarised in *The Origin of the British Flora*, by Mr. Clement Reid. A detailed account would be out of place here, but reference may be made to some of the districts yielding arctic plants.

It is obvious that the number of arctic horizons in Pleistocene and post-Pleistocene deposits cannot be indefinite, and therefore some of the arctic beds in peat and alluvial deposits may be contemporaneous with either one of the arctic zones in the

Scottish peat mosses. For the purpose of this paper the post-glacial deposits containing arctic plants group themselves into two sets:

(*a*) With arctic plants lying between an upper and lower temperate bed.

(*b*) With arctic plants at the base overlaid by temperate deposits.

Type (*a*) may be considered first.

At Hoxne, in Suffolk, four distinct superposed strata containing plant remains have been described by a committee appointed by the British Association (6).

Since the deposits fill a channel eroded through the chalky boulder clay, the intercalated arctic plants must belong to late glacial times, long after the general glaciation of the country.

The sequence of the beds is as follows:

1. Brick earth and gravel with temperate plants.
2. Black earth with arctic plants.
3. Lignite with temperate plants.
4. Clay with temperate plants.

It is sufficient to point out that the basal temperate beds contain such southern forms as *Bycopus europæus*, *Rhamnus frangula*, *Sparganium ramosum*, *Sambucus nigra*, *Rosa canina*, whilst the arctic bed above contains *Salix polaris*, *S. herbacea*, *S. myrsinites*, *Betula nana*, to show that there is definite evidence in the south of England of a change from temperate to arctic conditions during the later stages of the glacial period.

Fossiliferous beds of sand and peat yielding some evidence of changes in condition have been described from Ballaugh, in the Isle of Man, by a Committee of the British Association (7).

In this case the evidence for a change from an arctic to a temperate flora is not so conclusive as at Hoxne. Sandy silt containing *Salix herbacea* amongst other plants is underlaid by loamy peat and chara marl, from which arctic plants are absent, although most of the plants belong to species of wide distribution. The presence of *Apus glacialis* in the bed containing *Salix herbacea* certainly points to colder conditions than the present.

Numerous sections have been described in which an arctic plant bed occurs at the base of the series overlaid by deposits containing a temperate flora.

In 1894 Bennie (8) described fossiliferous beds from Hailes, near Edinburgh, the species being determined by Mr. Clement

Reid. The lower beds rest directly upon the boulder clay, and contain *Salix herbacea*, *S. polaris*, *S. reticulata*, together with about twenty other plants, some of which certainly do not now occur in the same regions as the arctic willows. As the basal arctic bed occurs in a lacustrine deposit, it is perhaps possible that it contains fossils from slightly different periods. Be that as it may, it is certain that the arctic willows indicate a very different type of flora from the temperate bed above containing such temperate forms as *Sambucus nigra*, *Prunus spinosa*, *P. Padus*, *Rubus Idæus*, *Cratægus oxyacantha*. These plants occur mixed with others usually considered as weeds of cultivation, such as *Stellaria media*, *Æthusa cynapium*, *Lapsana communis*, which suggest that the temperate bed belongs to a comparatively late period. If there is no break in continuity between the basal arctic bed and the overlying deposits containing temperate plants and weeds of cultivation, the evidence tends to show that the arctic plants belong to a period much more recent than the retreat of the ice-sheet.

Similar arctic plant beds have been described from Corstorphine, Faskine (9), Dronachy (10), by Bennie, and from Crianlarich by Reid (11), the plants from the various sections having been determined by Mr. Clement Reid.

Numerous other examples might be quoted from the lists given by Mr. Clement Reid (11), but enough has been said to show that arctic plant beds are of wide occurrence in Britain. The arctic plants of Hailes, Corstorphine, Dronachy, and Crianlarich apparently belong to the same stage, and the presence of *Salix polaris* in those deposits in the lowlands of Scotland suggests that they can hardly be younger than the first arctic bed underlying the Lower Forest in the peat mosses.

The section at Hoxne, where an arctic bed overlies a deposit containing temperate plants, gives the same sequence as the south of Scotland and Shetland peat, where the Lower Forest is overlaid by an arctic zone, though the fact that the Hoxne deposits rest upon the chalky boulder clay and the southern upland mosses upon morainic material of a later stage makes it probable that the Hoxne temperate bed is older than the Lower Forestian. If that be so, the arctic bed at Hoxne might still be contemporaneous with the first arctic bed of the peat mosses.

There can be little doubt that the lower bed at Hoxne

represents a warm interglacial stage, showing a very different set of conditions from the beds above containing *Salix polaris* and other arctic plants, and the events which would produce such a total change in the flora in the south of England must have been widespread. The suggestion made by Lamplugh (12) that the arctic flora might have lingered on and reinvaded the area formerly occupied by a temperate flora without any widespread change in conditions is surely due to a misconception of the present distribution of these plants.

It is quite certain that *Salix polaris*, *S. herbacea*, *S. myrsinites*, *Betula nana*, and such temperate plants as *Rhamnus frangula*, *Rubus Idæus*, *Rosa canina*, *Sambucus nigra*, *Corylus avellana*, *Taxus baccata*, did not grow at the same time over the lowlands of the south of England. Whether the precipitation during the deposition of the arctic bed was great enough to produce glaciation on elevated ground in the north of England and Scotland the plant deposits do not tell us, but we may be certain that an arctic climate prevailed at that time. If, then, from its position upon the chalky boulder clay, the Hoxne temperate bed is older than the Lower Forestian in the peat mosses, it carried the alternation of temperate and arctic phases to a still earlier stage—though a stage which all will agree is later than the last ice-sheet. It is true that evidence of actual glaciation can only be given by glacial deposits, but changes of temperature must be reflected in fossiliferous deposits.

The Relation of the Strata to the Glacial Succession.—It is evident that the peat mosses do not give any information about the chain of events during the maximum glaciation of the country, and it is immaterial whether we regard the morainic material—upon which so many of the older peat mosses in the south of Scotland rest—as the deposits of the waning ice-sheet of maximum glaciation, or as the deposits of an entirely distinct glacial stage separated from the ice-sheet by a warm inter-glacial phase. The fact remains that the first arctic bed contains an arctic-alpine flora which existed over wide areas near sea-level. It is, of course, impossible from the evidence of the plants to say whether all traces of glaciation had vanished from Britain at that time or whether certain regions were still under ice. An entirely different flora makes its appearance in the Lower Forestian; not only are all arctic-alpine plants absent, but the flora is made up of well-grown

trees and an assemblage of plants quite typical of any marshy lowland forest region in Britain at the present time.

If it be contended that the Lower Forestian is due to local changes in climate—such as variation in snowfall, direction of wind—how is it that the bed maintains its character not only in the south of Scotland, but also in the Outer Hebrides and Shetland Islands?

If the succession of the first arctic by the Lower Forestian, lower peat bog, and second arctic bed were really due to local causes, widely separated districts should show different successions; while, for instance, tundra vegetation would be represented in one district, the remains of a forest vegetation would occupy the same horizon in another. But this is not the case, for nothing is more striking than the continuity of the horizons. The chief points for consideration may be stated as follows:

(*a*) *First Arctic Bed.*—Lower limit of arctic-alpine vegetation depressed to sea-level.

(*b*) *Lower Forestian.*—Upper limit of deciduous trees raised to *at least* its present level.

(*c*) *Second Arctic Bed.*—Lower limit of arctic-alpine vegetation depressed to sea-level.

(*d*) *Upper Forestian.*—Upper limit of trees raised to over 3,000 ft.

These changes are post-glacial in the sense that they occurred later than the last ice-sheet. It is difficult to reconcile these changes with the "gradually waning glaciation, during which there were occasional local advances of the mountain-glaciers in their glens due to temporary increase of snowfall" suggested by Lamplugh (12). The beds rather indicate a definite sequence of events which took place simultaneously over the whole of Britain. Local changes of snowfall and local retreat and advance of glaciers almost certainly occurred during the later stages of the glacial period; but these could hardly bring about the widespread alternate depression and elevation of the limits of an arctic-alpine flora shown by the peat. It matters little whether these stages are spoken of as local changes during the waning glaciation or are expressed as glacial and inter-glacial stages; the fact remains that the climatic fluctuations were lengthy and pronounced enough to change the distribution of the flora in the north of Britain.

As the arctic beds contain plants indicative of cold and wet conditions, the probability is that glaciation took place in elevated regions during their deposition. The Lower Forestian contains a flora indicating conditions *at least* as temperate as the present day, and the Upper Forestian shows an elevation of the upper limit of forest far above that of the present day.

In Sweden a similar elevation of the upper limit of forest to the extent of 1,100 ft. (300 m.) took place during post-glacial times, and Gunnar Andersson concludes that the arctic-alpine flora then disappeared from the lower mountain ranges. Observations in Scotland would place the difference between the upper limit of trees during the Upper Forestian and at the present day as not much less than 2,000 ft. in the Highlands; in Cumberland and Westmorland at rather more.

It is possible that glaciers still lingered on in many parts of the Highlands during the earlier stages of the forest periods; this would be more likely in the case of the Lower Forestian than in the Upper Forestian.

The question of climate during the Pleistocene epoch has been discussed by Harmer (13) in an interesting and suggestive paper, and the conclusion is reached that a change in the direction of prevalent winds, due to different relative positions of areas of high and low barometric pressure, may account for the comparatively low temperature and high precipitation during some stages of the Pleistocene period.

The observations from Shetland certainly show a difference in the direction of the prevalent winds during the Lower Forestian period.

While it is difficult to reconcile the several stages in the peat with the theory of a single glaciation, the whole of the peat beds agree very closely with the scheme of classification proposed by Geikie (14). In that scheme the first arctic bed and lower peat bog would mark the gradual passage of the Mecklenburgian stage into the Lower Forestian; the second arctic bed would represent the Lower Turbarian; and the Upper Forest in the peat would correspond with the Upper Forestian or fifth inter-glacial stage.

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THE DUAL FORCE OF THE DIVIDING CELL

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In giving such an explanation of the present state of our knowledge of the forces involved in karyokinesis as will be intelligible to the readers of Science Progress, I shall suppose these to belong, on the one hand, to those interested in biology with a superficial acquaintance with physics, and on the other to the physicists with but a scant knowledge of biology. The task is no easy one: when approaching the problem from the biological side, I found that to deal with it I had to steep myself in Faraday's conception of lines of force till I could, so to speak, handle them freely; while I found my physical friends and counsellors most unwilling to tackle the explanation of processes whose sequence had mainly to be inferred from the co-ordination of innumerable fixed microscopic sections. To do my best will still, I fear, leave the following pages somewhat hard reading for both categories of readers.

Hermann Fol in 1873 gave the first account of the "mitotic" figure of the dividing cell, so named some years later by Flemming, because at this stage the plastic cytoplasm exhibits a definite threadlike structure. He wrote: "On either side of these remains of the nucleus are seen aggregates of plasma, closely associated granules which form two starlike figures. The rays of these stars are formed of the granules, serried into straight files. Several of these files stretch in bows from the one star or attraction-centre to the other. The whole picture is extremely clear, and has a vivid resemblance to the way in which iron-dust strewn between the two poles of a magnet arranges itself. . . . I rank myself entirely on the side of Sachs's theory of cell-division ('Furchung') by centres, not at all, I may say, on theoretical grounds, but because I have *seen* these centres."

Fol's observations have been followed and confirmed and

extended by many others, and we can now give approximately the whole story of cell-mitosis,[1] its antecedents and its consequences. We prefer to take for description the cells of Higher Animals—Metazoa—where the appearances are more complete than in Flowering Plants, as shown in fig. 1.

In A the cell is "at rest," *i.e.* performing its routine duties; the nucleus is seen to have at one side of it a small rounded body, the centrosome, with two central dots of denser matter,

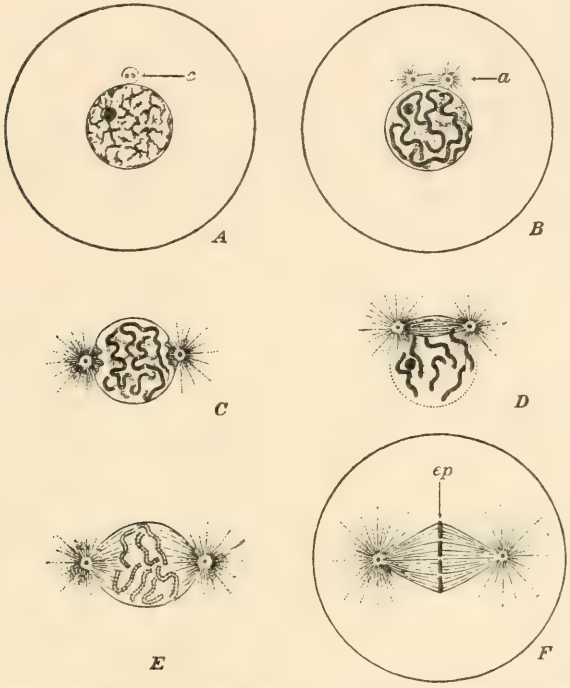

FIG. 1 (a).—Diagrammatic history of cell division in Echinoderm embryo (from *P.R.S.*, after Wilson). For explanations, see text.

the "centrioles" (*c*). In B this structure has divided into two small spheres, the "centrosomes," each with its centriole; and we already see the likeness of the magnetic field, for the ambient cytoplasm has developed a thread-structure, radiating into stars at the outer sides of the centrosomes, and uniting

[1] The more usual term in English, "karyokinesis," is not so convenient, since the kinesis is as much or more that of the extranuclear protoplasm ("cytoplasm") as of the nucleus; "mitosis," which means resolution into threads is far more apt.

their inner sides by a spindle formed of these threads. In C, D, the figure has grown; in C the nucleus occupies the middle of the spindle; in D it lies to one side of it, and the nuclear wall has disappeared on that side. In E the figure has enlarged still more and the nuclear wall has quite disappeared. The spindle persists and elongates in G, H, I. It is lost in J, on the completion of the process. It will be noticed that the contents of the

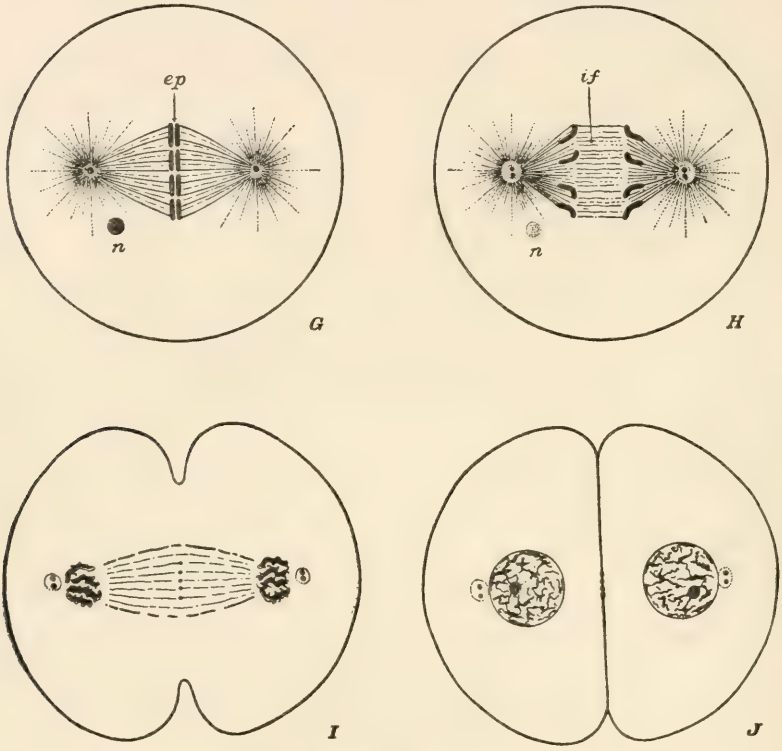

FIG. 1 (β).

nucleus arrange themselves so that by the time C is reached they are represented by thick threads: these take up certain dyestuffs readily, and are hence termed "chromosomes." In E it will be noticed that each chromosome has split along its whole length into a pair of daughter chromosomes. In F these are shortened and assembled at the equator of the spindle figure into what is called the equatorial plate (*e.p.*) In G and H the two sister halves of each chromosome separate and glide along the threads of the spindle towards the nearer centrosome. Sometimes

certain threads are attached to these daughter chromosomes and shorten and thicken during their retreat or "discession": always *some of the spindle threads remain unbroken and continuous across the equator.*

The daughter chromosomes of either side, on arriving in the neighbourhood of the centrosomes, aggregate together to constitute the daughter nucleus or new nucleus. Meantime the centriole has divided.[1] Cell division may accompany or follow the later stages of the process (H); but may be quite independent thereof. Thus many cases are known in Plants (*e.g.* the endosperm formation of Vascular Plants), Animals (*e.g.* the earlier stages of segmentation of the oosperm), and Protists (*e.g.* schizogony of Sporozoa), where the nucleus divides by mitosis repeatedly, so as to give rise to a multinucleate mass of protoplasm—the "apocyte"; and, on the other hand, such a multinucleate structure may ultimately be resolved into uninucleate cells by simultaneous or progressive segmentation of the cytoplasm around the single nuclei, without any mitotic phenomena whatever. We infer that the mitotic process is independent of cell-division. We term the force manifested in this process "mitokinetic force," or "mitokinetism."

The function of mitosis has been clearly recognised by all, and is, as expressed clearly by Wilson, that of effecting the "partitive" division of the chromosomes. It is evident that every unit of the original chromatic rod when split contributes one-half to either daughter nucleus—as if, in halving the contents of one's purse, one halved every individual coin.

The mechanism involved in mitosis has been variously interpreted: Klein, Boveri, Van Beneden, have referred it to the muscular contractility of the threads, pulling the chromosomes to the nearer nucleus. But in all divisions some of the threads remain till the end extending from pole to pole across the equator, and it would be necessary to explain their function, and to assign one different from the half-length threads supposed to pull: while in many cases, notably in plants, the threads all extend from pole to pole and the chromosomes merely glide along them, so that there can be no question of muscular contractility. This explanation, therefore, fails.

[1] Of course, for simplicity's sake I deal here only with the ordinary nuclear division: in "meiotic" division the function is other; but the mitotic mechanism is the same.

Again, Meves and others have suggested that the fibres from the one centre push the chromosomes across the equator to the other. The continuity of *some* of the fibres in certain cases, and of *all* of the fibres in others, is equally valid against this view; which lacks all probability, moreover, since the threads are certainly flexible, and quite unfitted for the *rôle* assigned to them.

These grossly mechanical forces we may call "linear" forces, unchanging in intensity along the line of push or pull. We leave them, and now pass to a more subtle group, the "centred" or "Newtonian" forces. With these the action radiates from a centre, and in a uniform medium changes in intensity inversely as the square of the distance from the centre. Of these are gravity, electrostatic force, magnetism, molecular osmotic attraction; and obeying similar laws are radiant energy, the flux of heat either from a calorifer or towards a refrigerator, the steady flow of liquid, either from a source or toward a sink, and the molar flow of osmotic currents. Gravity reveals no trace of bipolarity: for "negative gravity" and its effects we must turn aside from the facts of Nature to the imaginative pages of Frank R. Stockton; and the effect of a second gravitating body is obtained by arithmetical summation. The other phenomena admit centres of opposite sign, whose joint effects are their *algebraical* sum: positive and negative electricity, north- and south-seeking magnetism, calorifer and refrigerator, source and sink of stream-lines, centres of greater and of lesser osmotic concentration than the medium.

Numerous attempts have been made to explain what we have called "mitokinetic force" or "mitokinetism" as a centred force, and to refer it to one of the well-known centred forces enumerated above. Thus Bütschli and Rhumbler refer it to osmotic diffusion, Stanislas Leduc to osmotic currents, Frank Lillie and Gallardo (in his recent works) to electrostatic displacement.

The theory of the distribution of "centred" or "Newtonian" forces in a uniform medium was worked out geometrically by Faraday: unwilling to admit of gravity and magnetism acting at a distance, he introduced the conception of a strain in the medium (which might be substantial or ether), by which the stress radiating from the centre was transmitted along

"lines of force." His conception was extended and developed by Clark-Maxwell, who writes: "If we draw a line such that at every part of its course it is coincident in direction with the force at that point, this line may be called a 'line of force,' since it indicates the direction of the force at every part of its course."[1] It will be noted that such a line is a geometrical line, not a material line. Maxwell also recognised that for a field of two "unlike" poles the lines have the distribution of stream-lines in liquid in relation to an upwelling source and an engulfing sink, and, like Kelvin, saw that this distribution was identical with the lines of the flow of heat in a conductor

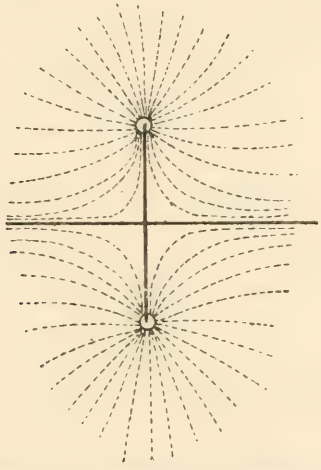

FIG. 2.—Diagram of the crossed field or antispindle, showing the directions of lines of force between two like poles. The lines shown are not "unit lines."

between a source of heat and a refrigerator; while the field of two "like" poles corresponded with the thermal field of two sources of heat, or two refrigerators, as the case might be.

Now, if we consider the force of gravity, which is, as we have seen, a simple force of uniform sign, and draw the diagram for two equal "centres" or gravitating spheres, we shall have this arrangement (fig. 2):

(1) Any heavy particle on a plane equidistant from the two centres—the "equatorial plane"—will move in a straight line,

[1] In fig. 2 we have approximately equidistant lines of force, but they do not represent the distribution of "unit lines" which we define below (p. 334). If these were represented it would be seen that the area between the centres is the weakest part of the field, and that midway the force sinks to zero.

bisecting that which joins their centres till it reaches the centre of figure; here, of course, no force is manifest, for the gravitation effect of the heavy bodies is here equal and opposite.

(2) The "polar axis" uniting the centres is another line of force; for a heavy particle lying on it will move along it to the nearer pole; or if at the centre will remain there.

(3) Besides these crossed lines will be a set of curved lines all convex to the equator and to the interpolar axis, but concave to the prolongations of the interpolar axis. Such a field has been termed a "crossed figure" or "antispindle."

If, on the contrary, the force is a dual or bipolar force, such as is represented by two conductors of opposite charges, by the two isolated poles of a magnet (if it were possible to

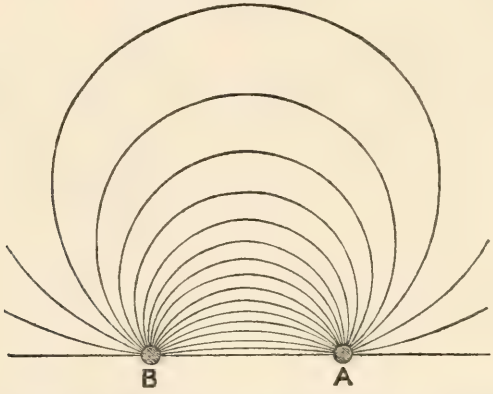

FIG. 3.—Field between two centres of opposite sign, upper half of axial section. The lines represent "unit lines." (From Watson's *Text Book of Physics*.)

obtain such), by a source of heat and a refrigerator, by an upwelling source and a sink, etc., then the distribution of the lines of force or flow is different:

(1) The interpolar axis and its prolongation still form one such line.

(2) The other lines of force run from pole to pole, as shown in the figure: they form a series of curves, all concave to the polar axis and convex to its ultrapolar prolongations.

(3) The lines starting from the inner half of each pole, and converging to it at either end, are what is called the interpolar spindle; the others, of which only the slightly curved basal parts are seen within the limits of the figure, constitute the "circumpolar radiations" and "asters"; but there is no marked

boundary between spindle and asters, for the rays of the latter ultimately curve in to meet their fellows of the opposite side, though it may be at an infinite distance.

It is obvious that in the cell the original extranuclear spindle is formed on the pattern of our present field, constituting a "true spindle," centred on two poles of "opposite sign." Hence, until it can be shown that at some period in the process of mitosis a reversal occurs at one or other pole—a supposition which has no shadow of evidence for its formation—we must conclude that the cell-spindle through all its stages is the expression of a dual force centring on the two centrosomes, which are of opposite signs. This at once disproves theories based on conditions assumed to be similar at both centres: (1) Bütschli's and Rhumbler's theory of like osmotic tensions of the alveolar cytoplasm around the two centrosomes; (2) Leduc's later view[1] of diffusion currents centring similarly about both centrosomes; (3) Frank R. Lillie's and Gallardo's later view of similar electrostatic charges on the two centrosomes of opposite sign to the intervening structures (including the chromosomes).

For our next step we must analyse the true nature of Faraday's lines of force, to see what they are and what they

[1] Leduc's earlier view was as follows: he found that visible diffusion currents pass in a solution between a centre of concentration and one of dilution, and that these follow the lines of a bipolar spindle. Thus into a drop of dissolved saltpetre lying flattened on a slide, and containing light bodies such as blood corpuscles in suspension, he introduced at one end a crystal of the substance and at the other a droplet of water, and obtained a beautiful spindle, which he photographed. That this explanation cannot apply to cell mitosis is certain, for the osmotic phenomena are of like kind in both centrosomes of the cell. This is admirably demonstrated in the gigantic cell-figures of the little marsh-worm, *Rhynchelmis*, which in the segmenting egg are just visible to the myopic eye, and whose changes have been fully worked out and portrayed with absolute accuracy by Véjdowsky and Mrázek. I have had the honour of being allowed to control the figures by inspection of the original specimens through the great kindness of these authors. Leduc, having been convinced by this reasoning, put forward the second hypothesis which we have just dismissed as equally untenable. Rhumbler attempted to demonstrate the kinematic paradox that a field centring on two "like" centres might, under certain circumstances, assume the "spindle" character. He placed a hexagonal elastic network on a ring over a flat plate, and through two holes pulled down the network, and found that the middle row, one mesh wide, was narrower next the centres of traction and wider in the centre, resembling a spindle. This appearance is a necessary consequence of the coarse structure of the net—it is a mere "grain structure." But looking outside this central row, we see at once that the general lines of tension form a figure which is essentially that of the crossed field or antispindle.

are not. From Clark-Maxwell's definition they are purely geometrical abstractions, like "rays of light" in geometrical optics; and in this sense there is an infinite number of "lines" traversing every field, just as there is an infinite number of "rays" in every beam of light. But we may give a quantitative meaning to both terms by a simple convention: just as we may say that the brightness of the illumination of a plane surface is proportional to the number of "unit rays" that fall vertically on it per unit of area, so we may say that the intensity of a force across any region of a field is proportional to the number of "unit lines" that cut normally the unit of area in that region. This is, indeed, largely the basis of the calculations of the electrical engineer; the C.G.S. "unit line" will exert a dyne

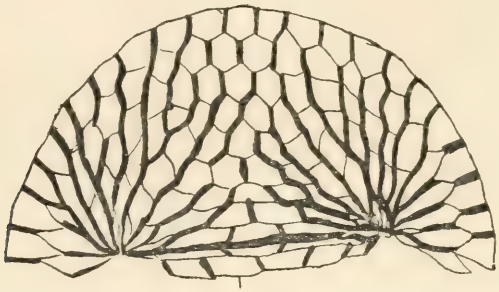

FIG. 4.—Rhumbler's net, pulled in at two centres; the direction of the lines of force indicated by thickenings (modified from Rhumbler and Hartog).

per cm. square; but of course we might take the microdyne per micron square as the force of our unit line, etc.

Turning to Gallardo's earlier view, that the mitotic figure represents the lines of force conditioned by a dual or bipolar force centred on the centrosomes, as two opposite poles, we find that this is inconsistent with Faraday's treatment, which only dealt with abstract geometrical conceptions. To render it applicable to the material conditions of the cell, I was obliged to amplify it by introducing from the domain of electricity and magnetism the conception of relative permeability of different substances, with the recognition of an undescribed configuration of matter, material "chains of force" due to redistribution of substances of unequal permeability in a field of force. Thanks to this enlargement, we shall find that Gallardo's explanation no longer presents those gaps which had hitherto invited the attacks of plausible opponents, and that the *à priori* arguments

they put forward against the theory have actually proved to be additional supports thereto.

Of course, abstract lines of force in a uniform medium are necessarily invisible to the eye. The nearest approach to rendering such visible is with transparent dielectrics in an electrostatic field; where, by the use of polarised light, we can demonstrate that the medium is under strain along the lines of force—and this is all that can be seen, even indirectly. The only way to see the course of the lines is to render the medium heterogeneous, and this must needs render the field no longer uniform—a truism, which has been much ignored. We do this for magnetic fields by the use of a small pivoted needle, too small in relation to the size and strength of the field to sensibly alter the direction and distribution of the lines: the needle sets everywhere tangential to the direction of the line that passes through its pivot. Another approximate mode is the familiar one of shaking magnetic dust in air on "rough" (*i.e.* not smooth frictionless) paper; the powder settles in lines running approximately along lines of force. Faraday already recognised that the presence of the dust altered the distribution of the very lines of force which they were used to demonstrate; but since in elementary physical text-books approximate statements are frequently used without due caution, it is not astonishing that biologists should have accepted such as complete, and attempted to refute Gallardo's approximate statement by applying the canons of lines of force to the visible mitosing threads of the dividing cell.

The need of using a heterogeneous mixture to model the cell-field was felt very early indeed. In 1876 A. Giard, already a brilliant young professor, keenly alive to the theoretical possibilities of new discoveries, wrote in an abstract of the then new facts of mitosis:

> L'explication physiologique du phénomène . . . doit être evidemment cherchée parmi les phénomènes physico-chimiques et la production de pôles électriques ou électro-magnétiques dans le noyau. Peut-être arrivera-t-on à mettre expérimentalement en évidence ces curieux processus en employant des sphères liquides en suspension dans un autre liquide, comme le faisait Plateau, mais en mélangeant ces liquides de substances fortement magnétiques et capables d'acquérir des pôles sous l'influence d'aimants puissants. Il y aurait tout un ordre de recherches à entreprendre dans ce sens (*Bull. Sc.* vol. vii. 1876, p. 258).

Nevertheless it was not till twenty years had passed, in 1896, that this mode of experimentation was taken up by his pupil, Angel Gallardo, whose previous training as a civil engineer had doubtless made him eager to utilise practical tests. Like Giard, Gallardo must have felt unconsciously the inadequacy of the abstract lines of force; but the only advantage that he claimed for his experiment (utilising the electrostatic field, and obtaining therein "chains" of sulphate of quinine suspended in turpentine), was that it represented the cell-field in three dimensions, instead of in two only, as in the magnetic models of dust on rough surfaces previously utilised.

To analyse the nature of the dust-lines or the quinine threads we must consider what is meant by relative "permeability" to such forces as magnetism or statical electricity.

If in front of a magnetic pole we interpose a block of soft iron, we find that the attractive force on a small piece of iron some distance off is increased, just as if it had been brought nearer to the magnet in air (or vacuum). In the same way, if we place a block of sulphur, or still better, glass, between the knob of a charged Leyden jar and a suspended pith-ball, we find the attraction of the pith-ball is increased, just as if it had been approximated in air (or vacuum). We say that the glass and sulphur, and the iron have greater permeability, electrostatic or magnetic respectively, than air. We cannot enter here into quantitative details, but if we take vacuum (*i.e.* ether) as having a permeability of 1 in both cases, soft iron has a magnetic permeability of several hundred or several thousand, glass an electric permeability of 6, an insulated conductor a permeability of infinity. Gravity alone among the forces we have considered is equally permeant to vacuum (ether) and to all known substances.

A permeable *particle* of negligible volume tends to orient itself in a field, so that its longest axis lies along a line of force, and if free to travel to pass along it to the nearer pole.

A permeable *body* in a field tends to pass to the position where it will enclose the maximum number of unit lines of force—*i.e.* to the strongest part of a field: thus a soft iron rod is sucked into a solenoid of wire through which a current is passing.

If a body of high permeability be introduced into a field occupied by a medium of lower permeability, the lines of force

on either side will converge inward—be "refracted" to crowd into the body; and if its permeability be infinite, they will enter it normal to the surface (fig. 5).

If we shake up fine magnetic dust over a rough surface, we have a dust-cloud, in which the particles can turn lengthwise to the lines of force; and if the cloud were permanent they would float along the lines to the nearer pole; but falling immediately as they do, they are retained by the friction of the surface in the position which they had momentarily assumed.

If now we suspend the magnetic dust in a viscid liquid, the particles arrange themselves loosely into filaments extending from pole to pole as a spindle with circumpolar radiations; but

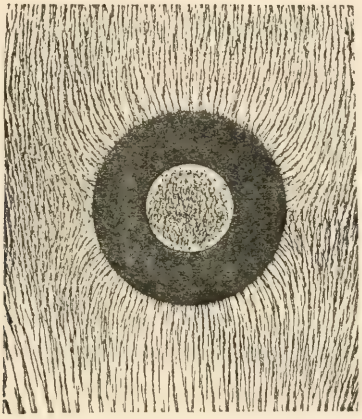

FIG. 5.—Magnetic dust-chains on paper showing (*a*) refraction into and out of an interposed inductor or more permeable body—an iron ring; (*b*) screening action of a hollow inductor on the space within.

these filaments remain stretching across because of the viscidity of the medium, corresponding to the friction of the surface in the previous case. I have called this configuration of matter of filaments of more permeable material segregated from admixture with a less permeable fluid medium under the stresses of a centred force, "material chains of force," or, simply, "chains of force." Such chains in a viscid medium may be regarded as flexible bodies of higher permeability than the medium (or briefly as "inductors"), and have characteristics of their own.

(1) Owing to their greater permeability they contain more unit lines of force per unit of cross-section than the surrounding medium.

(2) They may, and do, anastomose at the moment of segregation to form a network with rhomboidal meshes with the long diagonal lying along a line of force.

(3) They have great permanence and tenacity; they can be deflected by currents or by a stick; if ruptured, they shorten up towards the nearer pole, thickening as they do so (just like the "short filaments" in some mitoses).

(4) The explanation of the tenacity of the filaments is that the force tending to separate any two adjacent particles is very small, while the viscosity of the medium is very large. In the same way, with the magnetic dust-paper model the friction on the paper is enough to keep the threads from breaking up so long as there is no shaking.

(5) They may overlap at different levels, so as to decussate or interlace.

(6) If the mixture lies in a vessel that is rotated in a field, they lag behind the medium, and form *ſ*-shaped spirals centring on the poles. (By the use of a solidifying medium, such as melted jelly, their position at the moment of solidification can be fixed for photography.)

Every one of these six phenomena has been observed in some case of mitosis, and most of them are general. All have been declared to be incompatible with the theory of the dual force centred on the centrosomes; whereas the incompatibility is only with the behaviour of abstract geometric "lines of force," with which we now see the plasmic chains are not identical. Thus one series of objections to Gallardo's first view have now, by our enlargement, fallen to the ground.

Another difficulty has also arisen from too ready an acceptance of an abstract representation of a material arrangement. When the physicist discusses fields of force, he usually avoids complications by treating them as of unlimited extent, and as dependent only on the figured centres. In an unlimited field, as we have seen, all the lines of force are concave to the interpolar axis; whereas in the cell the polar radiations are often straight, or even have a reversed (*adossé*) curve, turning their backs on the spindle-chains to become concave to the ultrapolar prolongations of the axis. We can shed light on this by examining theoretically or practically the effect of limiting the magnetic field by a boundary of highly permeable matter, such as an oval "mask" of charcoal iron. In this case the astral rays, whether on paper or

in liquid, assume the direction of those of the cell, and meet the mask nearly radially at every point (fig. 6). From this we must infer that the boundary of the cytoplasm (" Haut schicht ") is of highly permeable matter.

Moreover, in such a case the lines of force of the asters, instead of passing away to meet at indefinite distances, pass into the permeable envelope to meet therein.

By this action of a permeable envelope it serves as a screen; it prevents similar forces in a field outside acting on the space within, or interfering with an internal field of force: this screen action is recognised by the practical electrician, who has found that the best way to protect a building from lightning is to screen it by a cage of connected wires which are conductors

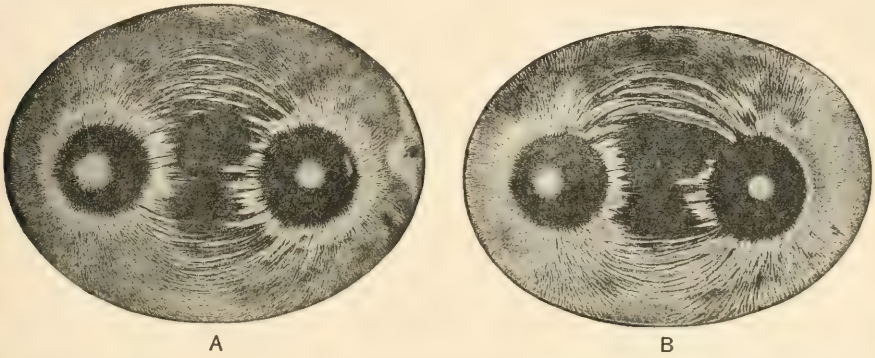

FIG. 6.—Axial section of a limited magnetic field of force; the medium being powdered magnetite in glycerine; the effect of the permeable boundary in deflecting outwards the astral rays is well shown with anastomoses and decussations of the chain: A, immediately after the formation of the magnetic field; B, after the action of a more intense field, showing the sidling in of the outer chains of the spindle to leave a Bütschli's space on either side.

(*i.e.* inductors of infinite permeability). Our next deduction from this screening action is that the centrosomes must at least be bounded by a highly permeable layer, even if their whole substance is not equally permeable, for no influence of the cell-field's action on the alveolar internal structure of the centrosomes is visible at any moment (fig. 10). Similarly, the nuclear wall must be highly permeable, and serves as a perfect screen so long as it remains complete.

Years ago, Leopold Errera, whose loss we all mourn, left plants with their growing points in a very strong magnetic field, and found that there was no distortion; and this experiment

was held to prove that the cell force was not identical with magnetism. But since, as we have shown, the cytoplasmic boundary is an efficient screen to mitokinetism, as is, moreover, manifest in the fact that cells in juxtaposed cells have the axes of their spindles inclined at all angles, uninfluenced by any induction from their neighbours, it is obvious that if mitokinetism and magnetism were identical, the most powerful magnetic field could have no more effect than the neighbouring cell-fields. The real argument against the identity of the two forces is that if they were one and the same growing tissues would be strongly ferromagnetic, which they are not.

The threads of the cell-spindle tend to crowd inwards towards the interpolar axis, shortening and thickening as they do so: we have noted that this is the characteristic behaviour of conductors and inductors in the electrostatic or magnetic field. We can demonstrate this with our models of iron-dust in a viscid medium; if we use a strong field the outer chains sidle inwards towards the axis, shortening and thickening as they do so, thus accentuating the contrast between the spindle and the asters, and leaving on either side a relatively clear outer space (fig. 6, B). A similar space may often be found in cell-figures, and indeed has been actually named "Bütschli's space" by Rhumbler.

We now pass to the "polyasters," or cell-fields with more than two centres united by spindles. I indicated in a note in the *P.R.S.* that since writing the paper I had found additional light on this subject; and this presentation is an advance on what is given there. The idea of a "pole," a centre on which lines of force converge, all having their like ends upon it, is as purely abstract an idea as that of the lines of force themselves: this every student of magnetism learns at a very early stage. We may give precision to our ideas by calling a solid on which lines of force converge a "centroid"; and if all the lines have like ends thereon it will be a "pole-centroid." The centrosomes of an ordinary cell-spindle are, then, pole-centroids.

But if we consider the fact that lines of force are refracted towards the normal in entering a more permeable body from a less permeable medium (fig. 5), and similarly refracted away from the normal in quitting the more permeable body, we see that there is another type of centroid, with lines of force converging upon it on the one side and diverging from it on the other—a centroid, we may say, on which two sets of lines of force converge,

but with ends of "unlike" sign. In other words the interposition of a body of high permeability in a field of force determines the production of two spindle-ends converging on it. Such a body with such a function we may term an "interposed" or a "bipolar centroid." Thus, if we take an ordinary spindle (magnetic) and place midway a piece of charcoal iron, whatever be its form, this will divide the spindle into two spindles, each centring at one end on an original pole-centre, at the other on the interposed bipolar centroid. If we displace the interposed iron sideways from the equator we shall obtain a triaster of three centroids joined up by consecutive spindles—the longer spindle between the two pole centroids, and two shorter inter-

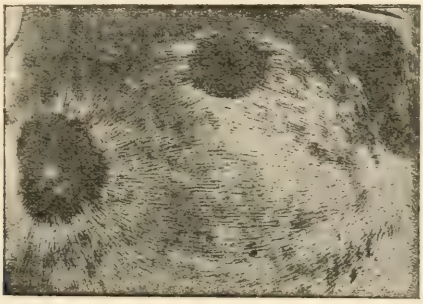

FIG. 7.—Magnetic triaster (in glycerine), formed on two pole-centroids and one interposed or bipolar centroid.

mediate spindles, each starting at a pole-centroid and ending on the bipolar centroid (fig. 7).

But there is another way in which we can realise a triaster. If we consider a field in which the lines of force have a concentric arrangement—as, for instance, a magnetic dust-field traversed by a central electric current—and we interpose in the field at equal distances three balls of charcoal iron, we shall have no pole-centroids, but only three equal and equidistant bipolar centroids, with the original concentric circles changing into three consecutive spindles joining up the three centroids. I have modelled a section of such a field (fig. 8).

At first sight this interpretation, assigning a secondary *rôle* to the centrosomes, will appear strange to the layman who is accustomed to think of the poles as the sources of the forces of the field; but the physicist nowadays, as pointed out by Gallardo, will accept this as the correct view to take.

If we have a tetraster of four consecutive pole-centroids[1] at the apices of a square, and introduce a permeable sphere at its centre, we obtain a beautiful pentaster with five centroids and eight spindles (fig. 9, A).

Another polyaster might be obtained if we could place four like poles at the vertices of a tetrahedron, and a permeable sphere at its centre; the actual plane model is shown below (fig. 9, B).

This is perhaps the best place to consider the "false

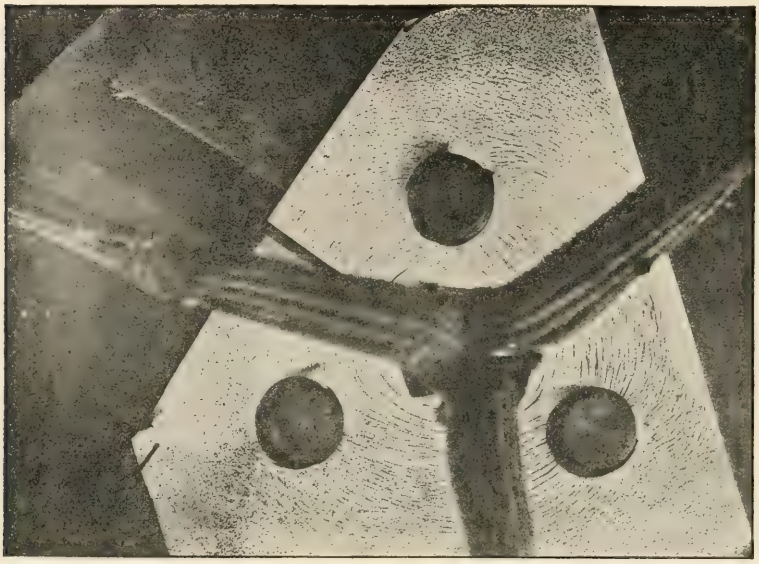

FIG. 8.—Triaster (dust on paper) formed in a circular field on three interposed centroids. The current passed up through three meridional bundles and down through the axial bundle shown; and the paper lay in the equator of an approximate sphere.

spindles" of Rhumbler, Leduc, and Gallardo (in his second interpretation). Leduc has made models with diffusion currents

[1] The odd-figures, the tri- and pentaster, are the most important from a theoretical point of view; for Rhumbler, not recognising the action of an interposed centroid in determining the insertion of spindle-ends, had declared that magnetic fields—and indeed this reasoning applies to all dual forces—could not possess an odd number of centres and of spindles. "Magnetic lines of force can never form three spindles between three consecutive poles . . . three adjacent poles, even when there are more than three poles in the field, can never be joined up by three spindles" ("Mechanische Erklärung der Ähnlichkeit zwischen Magnetischen Kraftliniens Systemen und Zelltheilungsfiguren," *Arch. Entwicklungsmech*, vol. xvi., 1903, p. 482).

in this way. He let a drop of solution spread out on a slide so as to form a flattened plano-convex lens, and at the two ends introduced "similar" osmotic centres. Under these circumstances the stream-lines from either centre assume the dis-

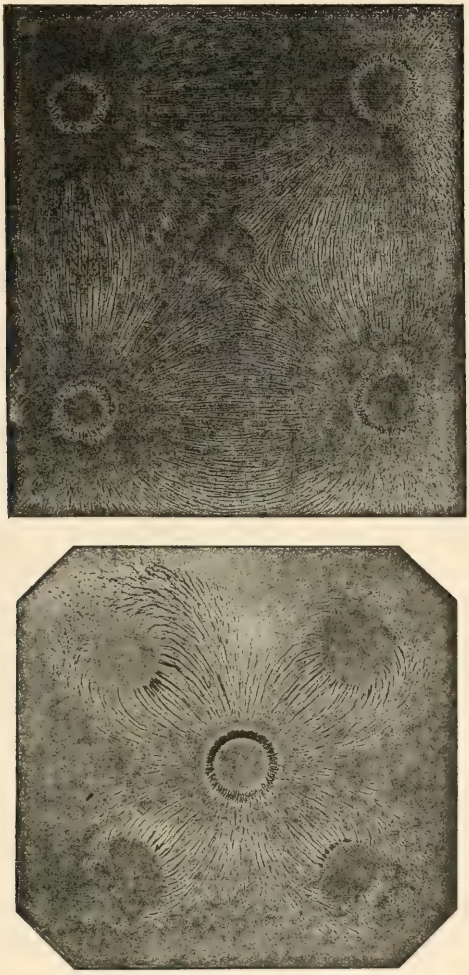

FIG. 9.—Polyasters of magnetic dust. B represents in a plane the figure of four like poles and a central inductor such as corresponds to the tetrahedral figure of the heterotype division in Liverworts, where the chromosomes represent the central inductor.

tribution of half-spindles, with their lines concave to the axis but their basal ends at the equator *never blending*. The assumption of this form is due to the necessary constrained parallelism of the outermost stream-line to the boundary of

the drop, and to the inductive effect of the position of these outer lines on those within.[1] In a large cell the outermost spindle-threads may be quite remote from the cell-boundary; and, as we have seen, the threads are continuous across the equator, which is an impossibility in Leduc's model.

Gallardo, adopting a mode of experimentation suggested by Guébhardt, places two like poles of a battery on a horizontal metal plate in an electrolyte, and, midway between them, two wide strips of metal connected with the opposite pole, in the position of the already split equatorial nuclear plate (fig. 1, G). In this case electrolytic deposit takes place on the basal metal plate in successive zones corresponding to equipotentials, and the lines of force may be drawn by a series of curves cutting the zones at right angles—in terms of geometry the "orthogonal trajectories" of the equipotential zones. These lines of force so drawn form two half-spindles, centring on the two like poles, and with their bases resting on the strips of metal connected with the opposite pole. Here it is the presence of the strips that alters the distribution of the lines of force so as to make them simulate two halves of a spindle, and here again *the spindle is interrupted in the centre.* Though these two models give an approximate representation of the cell-figure at the moment of the splitting of its equatorial plate, yet even for this state they take no account of its continuous fibres from pole to pole, nor of the origin and growth of the cell-spindle as a true spindle from its first appearance. The two models are pretty paradoxes: they are nothing more.

It is always well to assume that capable workers have not gone astray without some good reason for their deviation. Why, then, should biologists again and again have sought to ignore the true bipolar character of the cell-spindle? One reason is the fascination of simplicity: they have sought to explain the complicated process of mitosis and of cell-division by a single series of forces. But still more important is one real difficulty arising in the "dual force" explanation that we have not yet touched. One necessary result of a spindle centred on two opposite poles is to tend to draw these two poles together, and to deform the cell into a biconcave disk like the red blood

[1] The distribution of stream-lines and of lines of force, etc., is always such as it would be if they repelled their neighbours—as if they exerted a pressure at right angles to their direction.

corpuscle of a mammal; whereas in the cell, as in the "false spindles," the poles themselves diverge during the process of mitosis. Clearly the fact is, the separation of the centrosomes during the growth of the spindle cannot be referred to our dual "mitokinetic" force, and we must seek another explanation. The bulging of the spindle-figure in the endosperm of flowering plants and other facts indicate that the outer zone of the spindle is a continuous membrane, semi-permeable to liquid, and that the cavity through which the spindle-threads run is turgescent; this is certainly one factor in the character of the growth of the spindle, and in the separation of the centrosomes. Moreover, the outer cytoplasm must also exert a tractive influence, pulling the centrosomes towards the periphery of the cell. We have

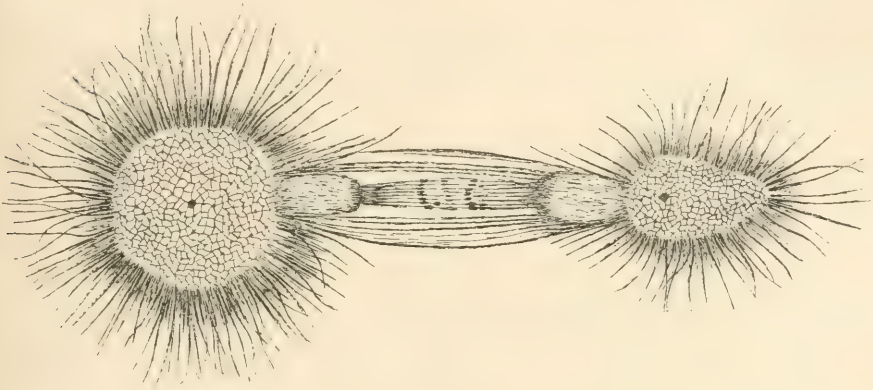

Fig. 10.

direct evidence of this in many of the cell-figures of the embryo of *Rhynchelmis* (fig. 10). Here the centrosomes are elongated by this pull and drawn out into doublets or "blobbed," the smaller blob being next the spindle, as if that part anchored by the pull of the spindle fibres had resisted the pull of the outer cytoplasm more than the section in direct contact with the cytoplasm.

The irregular distribution of the polar rays in *Rhynchelmis* points to the existence of cytoplasmic creep, which disturbs their distribution. Just so do currents deviate the magnetic chains in a glycerine field. The well-known spiral asters or polar fields in the segmenting egg of the slug (*Limax*) afford a still more striking proof of the activity of the outer cytoplasm during mitosis. Thus, far from referring all the complex of forces

involved in complete karyokinesis with cell-division to one force, we must regard even the simplest cases of mitosis as the resultant of two actions at least of different character: (*a*) the bipolar mitokinetic force, and (*b*) the homopolar traction of the cytoplasm on the centrosomes.[1]

We have now seen that the only adequate explanation of the mitotic figure is that it is a strain-figure under a dual force or polarised stress, and that the threads obey the same laws as flexible chains of force in an electrostatic or magnetic field; and we pass to the chromosomes, which are but lightly dealt with in the *P.R.S.* I have made experiments which show that the chromosomes can be represented in a magnetic field by floating chains of iron beads; that two parallel chains of magnetisable beads at the equator tend to separate and to recede to opposite poles, but if nearer the one pole they are both attracted to it and diverge as they come to it. Now Mme. Boveri has shown that when the assemblage of split chromosomes known as the equatorial plate is formed nearer to the one pole of the cell spindle, *all* the half-chromosomes pass to that pole, diverging much more strongly as they approach it. This result, which could be predicted as the necessary action in a dual field of force, is totally inexplicable in any other way.

Again, if we float on mercury two chains of steel beads, magnetised so that their like poles are all in the same direction across one another, or if we take chains of cork balls, each containing a steel rod magnetised in the same way, and float them in water crossing one another about the middle of the chain, they will diverge into an X; if they be attached at both ends, they will diverge into an ellipse, with its long axis parallel to that of the field; if they are attached at one end and cross in the middle, they will take the form of a ∝. The same would occur if the magnetised steel beads were replaced by soft iron beads, lying in the field of two opposite magnetic poles. Now all these associations are reproductions of figures shown by the pairs of split chromosomes as they lie about the equatorial plane of the spindle still attached by remnants of the viscid nucleoplasm or linin, before this bond finally gives way under the stresses of the field, and leaves each daughter

[1] A detailed discussion of the various processes involved in normal mitosis, with a full refutation of the single-force hypotheses, will appear shortly, in English, in the International Edition of the *Rivistà di Scienza.*

free at last to discede from its sister. We have here the experimental demonstration of the fact that the chromosomes are "mitokinetised" by induction in the place they occupy in the cell-field, and that this will account for the completion of their splitting and final discession, because they are composed of a substance more permeable to mitokinetism than any other element of the cell. We are perhaps justified in conjecturing, as I did nine years ago, that this susceptibility to mitokinetism is the function of the actual chromatic substance, which augments so enormously on the approach of nuclear division, and which diminishes during the intermediate periods of ordinary cell life: thus the important structures of permanent morphological value of the chromosome would be the achromatic substance, and the function of the chromatin would be mainly mechanical, subserving the partitive division in mitotic division. This view has since received independent advocacy from Boveri. I shall discuss it more fully in the *Rivistà di Scienza.*

But in the cell there is one essential point of difference from the conditions in our models: the more permeable substance is not merely precipitated from the medium once and for all; it grows at the expense of other substances in the cell. This is especially evident in the segmenting egg, with its enormous supplies of not-living food material. The different character of this permeable material of the cell-chains has long been recognised, and its function denoted by the terms "archoplasm" (Boveri) and "kinoplasm" (Strasburger), which have been applied to it. From the consideration of the work of Véjdowsky and Mrázek, it would almost seem certain that the centrosomes, so conspicuous in the animal cell, have for their chief function the metabolic processes that determine this growth.

In Metaphytes the centrosomes are, if present at all, exceedingly minute; and Anstruther A. Lawson has shown that the spindle-fibres take origin immediately in contact with the nuclear wall and extend thence into the cytoplasm, only slowly assuming the spindle-grouping. We may infer that the metabolic function of forming the kinoplasm lies in the centrosome in Metazoa and in the nucleus in Plants. As stated just now, the limiting membrane of nucleus and of centrosome behaves as if infinitely permeable to mitokinetism, and affords a perfect screen to its contained plasmatic structures; for these are as free from mitokinetic strain as would be the contents of a metal

sphere in the most powerful electric field. Gallardo was the first to note this, and the publication of Véjdowsky and Mrázek's figures have given the most striking confirmation to his theoretical anticipations. The *gebildete Laier* is so accustomed to the idea that the movable plates of an electrostatic field, the equally movable (though inseparable) poles of a magnet are the *sources* of the energy of a field, that it was natural to apply this inadequate conception to the cell-field in Metazoa, and to hold to it even after it became clear that it could not apply to Higher Plants. But the physicist will have no difficulty in accepting the view that the stresses of the strain-field are correlated with its condition of strain, and that the centrosomes are merely sources of supply of highly permeable material to hold and to convey that strain.

Finally, we must regard the processes in the mitotic cell-field as due to the combination of many factors. We may summarise them thus :

1. Mitokinesis is the expression of a dual strain-force, acting in a viscid heterogeneous medium, of which the more permeable constituent segregates out into chains of force, grouped into spindle and asters.

2. The centrosomes are infinitely permeable to mitokinetism. They are centres of like osmotic phenomena, probably conducing to the growth of the archoplasm of the chains of force.

3. Nuclear wall and cytoplasmic boundary are also highly permeable to mitokinetism.

4. The functions of the centrosomes are (i) to afford fixed points for the spindle ends; (ii) to provide for the growth of kinoplasm.

5. Ordinary cytoplasmic motion explains the growth of the spindle and the progressive divergence of its ends.

6. In the completion of the splitting of the chromosomes and the discession of the daughter halves, they behave exactly like flexible inductors suspended in a viscid medium in a magnetic field.

7. Mitokinetism is the force which determines the partitive division of the formed contents of the nucleus.

8. Polyasters, even with an odd number of centres, may occur in the fields of a dual force.

9. No theory of like forces at the centres of the cell-field will account for the typical spindle.

ERRATA.

THE SEQUENCE OF PLANT REMAINS IN THE BRITISH PEAT MOSSES.

Owing to the author's absence abroad, and the proofs not reaching him until after publication, several misprints occur in the text.

The following are the chief errata :—

Page 318, line 32, for *plot*, read *foot*.

,, 320, ,, 21, ,, *Bycopus*, read *Lycopus*.

,, 321, ,, 12, ,, *Stellaria media*, read *Chrysanthemum Segetum*.

Kelvin
Feb11,1904

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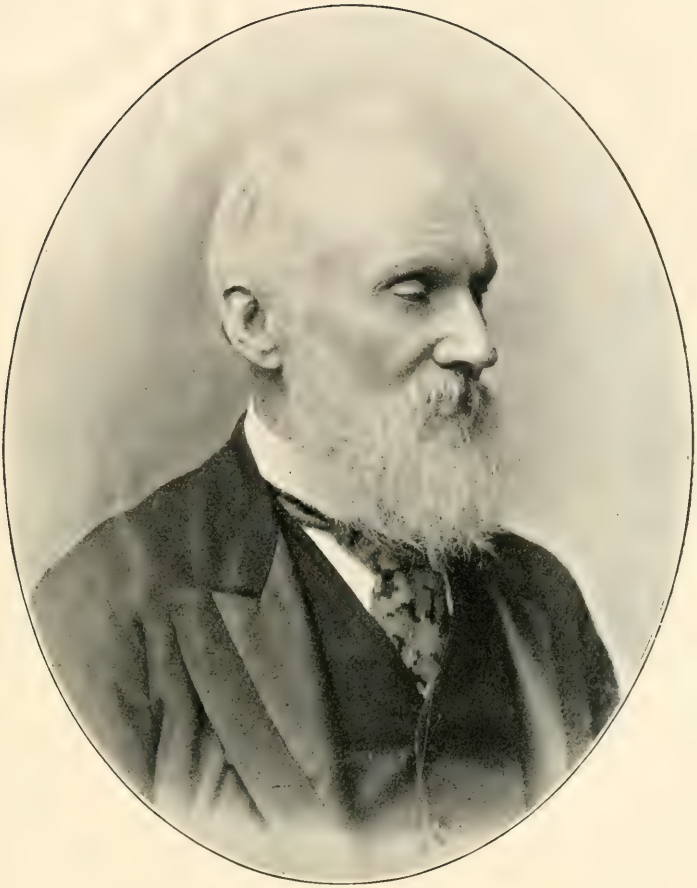

Kelvin
Feb 11, 1904

WILLIAM THOMSON

BARON KELVIN OF LARGS

P.C., O.M., G.C.V.O., F.R.S., F.R.S.E., LL.D., D.C.L.

BORN JUNE 26, 1824; DIED DECEMBER 17, 1907
BURIED IN WESTMINSTER ABBEY

On the death of Lord Kelvin there passed away one who will always remain identified with the remarkable progress achieved by science during the nineteenth century. At the celebration, in June 1896, in honour of the jubilee of his professorship at Glasgow, Lord Kelvin referred to his original contributions to science "as a record of persevering endeavour to see below the surface of matter." This endeavour resulted in profoundly modifying some of the conditions of life for many of the inhabitants of this world, in virtue of his extraordinary faculty of applying to practical matters the fruits of his researches. In

this connection it is not necessary to do more than refer to the great part he played in the development of submarine telegraphy, in the improvements he effected in the sounding plummet and the mariner's compass, in the invention of accurate and sensitive instruments for electrical measurements, and in the general advancement of electrical engineering. His researches on the tides added greatly to our knowledge, both theoretical and practical, of these important phenomena, and furnished another line of attack on the problem of solving the age of this earth.

In pure science, by his researches in thermodynamics, wave motion and vortex motion, Lord Kelvin advanced greatly human knowledge of the properties of matter. The whole civilised world recognised him as one of the most brilliant natural philosophers of all time, and now mourns his loss.

THE PHOTOGRAPHY OF COLOUR

By CHAPMAN JONES, F.I.C., F.C.S., etc.

Royal College of Science, London

I

As this problem has engaged the attention of innumerable workers for nearly a hundred years, and the best methods so far known are now carried out on a considerable scale, it is obviously impossible to deal with the subject with any approach to completeness within the compass of an article such as this. I propose, therefore, to consider the principles involved rather than the practical details, and to deal with the subject broadly rather than minutely.

It is worth while first to ask, What is meant by the expression "photography of colour"? There is no doubt whatever as to what it means in its simplest conception. Ordinary photography depicts form with an accuracy and minuteness that far exceeds the best handwork; and by special care—that is, the use of special lenses and of cameras made after the manner of surveying instruments—it is possible to get results that may be depended upon for surveying purposes. Not only is correct "drawing" inherent in photography, but also the rendering of light and shade—that is, the comparative luminosities of the various parts of the object, within certain limits that are well understood. The simplest idea and the most acceptable method of the photography of colour is that in which the colour of the object is reproduced as automatically and correctly as its shape, and shall be visible on ordinary inspection as the colours of a painting are. Such colour photography has been eagerly sought for but is as yet impossible; and if one is justified in judging of the future in the light of the past, it will remain impossible. There does not seem any line of work that can lead to such a result. From this point of view colour photography as now practised is always a compromise.

The methods of both the past and the present naturally

fall into two great classes, or, more correctly perhaps, a greater class and a lesser class. The less important division includes methods in which a single homogeneous surface is employed, while in the larger division the surface is multiple or non-homogeneous. The first is generally an attempt to get as near as possible to the simple colour photography described above, while the second is entirely indirect in that it does not aim at producing colour at all, but only at automatically locating suitable dyes or inks. We will consider the direct method first.

Dr. T. J. Seebeck, of Jena, in the year 1810 or thereabouts, while making some experiments as to the action of the solar spectrum on silver chloride, observed that the violet light of the spectrum produced a reddish brown substance sometimes inclining towards violet, that the blue light produced a blue substance, and the red a rose or lilac substance. If the silver salt had previously been exposed to light for a time, so as to darken it, there was a bleaching action where the red and yellow light fell upon it. It is hardly likely that he had in mind any photographic process whether in colour or otherwise, as photography at this time was not a practical art. Eight years before this Sir Humphry Davy had described at the Royal Institution the attempts of Thomas Wedgwood, which he had supplemented, to get a practical photographic method—a printing process as we should now call it—but their preparations were very lacking in sensitiveness, and no method of fixing them was known. Of those who were primarily concerned in working out practical photographic methods, the elder Niepce began his work in 1814, Daguerre in 1824, and Fox Talbot in 1833, and it was not until 1839 that their work culminated in serviceable processes.

Edmund Becquerel appears to have been the first to specifically attack the problem of the photography of colour. It is stated that he began his investigations in 1838, though he did not publish any results of them until ten years later. Although the earlier date was just before the methods of Daguerre and Talbot were published, there is no doubt that there was a general knowledge in scientific circles that something of the kind would shortly be made known, and that this directed the attention of many investigators to the possibilities of photography. But long before 1848 other workers had made observations concerning the photography of colour. Sir John

Herschel had repeated Seebeck's experiment; Daguerre and Fox Talbot had both observed that in some of their photographs a red object produced a red colour in the picture; and Robert Hunt had succeeded in obtaining colours on paper impregnated with various silver salts. Hunt put, for example, a prepared sheet under red, yellow, green, and blue glasses, and exposed the arrangement for a week to diffused light. The silver chloride "became red under the red glass, dirty yellow under the yellow glass, a dark green under the green, and a light olive under the blue." But with a sheet "differently prepared" he tells us he obtained "a very beautiful picture," in which the sky was crimson, stucco-fronted houses came out slaty blue, and the green fields of a brick-red tint.

Becquerel used silver plates and produced a layer of silver chloride on the surface of the metal, at first by the action of cupric chloride, but afterwards by the electrolysis of dilute hydrochloric acid with the silver plate as the positive electrode. The plates were treated until the very thin layer of the accumulating chloride on their surfaces had passed through certain definite colour-changes, and then washed, dried, and warmed. With these plates he reproduced, with a considerable measure of success, the colours of brightly dressed dolls and highly coloured designs besides the solar and electric arc spectra.

There were many others who busied themselves with experiments of this character at this time and for many years afterwards, making little variations and meeting with more or less success, sometimes propounding strange theories and endeavouring to justify them, and now and again expressing their hopes and almost their convictions that what they sought for was just coming within their reach. But their hopes were ill founded, for the work was purely empirical; they had no sound principles to guide them, and no real progress was ever made. Even the colours obtained were not permanent, and though some when considerable care was taken to preserve them lasted longer than others, the difficulty of "fixing" them, or rendering them even moderately stable, was never overcome. We shall shortly see something of the nature of the colours produced in these experiments.

If light waves are similar to the waves produced by disturbing the surface of water, as they are supposed to be, it follows that if a continuous series of waves is reflected back

upon its original path, the waves travelling in opposite directions will interfere with each other. It is clear that as they move in opposite directions each wave will alternately coincide with and oppose a wave of the series that it is meeting, and that where they coincide their moving power on the particle concerned will be added, and that where they are opposed the particle can obey neither impulse, and therefore remains stationary. There is thus produced a series of "standing waves," for although their crests rise and fall or move to and fro at (practically) right angles to the path of the disturbance, they move in neither direction along the path. The alternate crests move in opposite directions, and between each and the next there is a stationary point. If these conditions are realised in light waves, the light will be quenched at those points where the movement of the particles (of the luminiferous ether) is prevented, and there will result a series of layers of light with intervals of darkness half a wave length apart.

Dr. W. Zenker, of Berlin, in 1868 published a small volume, *Lehrbuch der Photochromie* (*Photographie in natürlichen Farben*), in which he examined in detail the methods, theories, and results of the work that had been done up to then in connection with the reproduction of colour. While satisfied that coloured light will under certain conditions produce something that reflects the same, or very nearly the same, colour as the incident light, he points out the insufficiency of the theories of the change that had been put forward. The colour of the incident light, though reproduced more or less in all cases, is especially noticeable when silver plates are used, as in the method of Becquerel. He then explains the nature of standing waves, and advances this as an explanation of the phenomenon. The silver chloride, especially if violet (that is, slightly reduced), is so affected by the light that metallic silver is produced in layers, with intervals of no chemical change which correspond to the parts where the light is quenched by interference. He supposed metallic silver to be produced because it is necessary for the reproduction of the colour that the product of the change shall be a good reflector. As to why reflecting laminæ of this kind should reflect only or chiefly light of the same wave length (or colour) as the light which produced the laminæ when they are illuminated by white light, he explains that light of a greater or less wave length than that of the original incident ray will be out

of harmony with the reflecting laminæ, so that the reflections from the various laminæ will be in dissimilar phases, and the resulting interference will cause this light to be more or less extinguished. But that part of the white light that corresponds in wave length to the original ray will be reflected at each lamina in such a manner that the difference in progression will always be equal to exactly a whole wave length, and therefore the light reflected from each surface will reinforce that from every other. He considered that this explanation followed from the wave theory of light, and required only one hypothesis, namely, that the product of the light action should reflect light strongly.

Although Zenker was not entirely correct and his theory did not pass unchallenged, his work eventually proved to be of great importance. Still, it was hardly appreciated at the time, and was apparently soon forgotten. Perhaps the method of its publication militated against its being widely known.

Lord Raleigh in 1887, and Prof. Otto Wiener of Aachen a few years later, both independently and without knowledge of Zenker's work, suggested that the production of standing waves might account for at least some of the results of the early colour photographs. But Wiener went a great deal further than this, and in 1895 published the results of an exhaustive examination of these methods, including the testing of pictures produced by them, to determine whether the colours were due to pigmentary matter or interference or both. He used a right-angled prism of dense glass with its three faces polished, placing the hypothenuse surface in contact with the spectrum photograph to be tested, with a liquid of high refractivity (benzene) between to exclude air, so that the refracting edge of the prism crossed the colour boundary. The colour was then viewed, with certain precautions, so that part of it was seen directly and part through the prism. With a pigmentary colour both parts remained of the same tint, but a colour due to interference was changed by the presence of the prism, so that, for example, yellow appeared bluish green. Wiener prepared some examples by Seebeck's method (precipitated silver chloride darkened by exposure to white light and then exposed to the spectrum), and found the red a rose-red, the blue greyish, and the green and yellow very poorly represented, if at all. He found these colours to be pigmentary. A modification, due originally to

Poitevin, but with slight improvements, was investigated. Silver chloride precipitated in paper was exposed to daylight in a solution of stannous chloride until darkened. It was then immersed in a solution containing potassium bichromate and cupric sulphate and exposed slightly moist. This reproduces all the colours more or less, but with a tendency towards a yellowish brown tint. These colours also are pigmentary. The colours produced by Becquerel's process, in which a silver plate has its surface converted into chloride by the electrolytic method, were found to be chiefly interference colours due to the action of standing waves, but there was pigmentary matter also present.

The colour obtained in these older processes being due entirely to pigmentary matter, except when a metal plate was used, the natural question is, What is the character of the pigmentary substance? Wiener found that silver subchloride was sensitive to all the colours of the spectrum as silver chloride that has been exposed to light is, and as these two substances are alike in other properties, there seems little doubt that silver subchloride is the colour-sensitive substance in these processes. Why it should be changed by coloured light into a substance that has some approach to the colour of the light that falls upon it is a problem still unsolved. But it seems exceedingly unlikely that any useful method of colour photography will be realised on this line of work, because the colours at their best are only approximately similar to the colour of the light that produces them; they cannot be fixed because the pigmentary matter is decomposed by solvents of silver chloride; the subchloride does not bleach to white in white light, nor is it itself black—two conditions that must be fulfilled in a material that is to reproduce colours by the direct action of light. Wiener suggested as the ideal material a black mixture of three differently coloured substances which are bleached to white by white light, and are sensitive in proportion to their absorption. In the next section the practical realisation of this principle will be described.

We have already seen that "standing waves" were predicted as a necessary result of the undulatory nature of light, and it appears that several physicists sought to obtain experimental evidence of their existence, but it was not until 1891 that Prof. Gabriel Lippmann of Paris was successful. If these stand-

ing waves could be produced in a photographic film, it was argued that deposits of silver should be obtained starting where the amplitude of vibration is greatest, with no deposit at the nodes, and that these layers would reproduce the colours that originated them when they were illuminated with white light and viewed under suitable conditions. This, therefore, would constitute a method of colour photography. It is obvious that for success the film used must be sensitive to all colours, it must have a good reflecting surface to send back the incident light, it must be transparent so that the reflected light may be as nearly as possible of its original intensity and that there may be a negligible amount of scattered light in it, and the sensitive material must be grainless, or very nearly so, for the layers of silver to be produced would be distant from each other, centre to centre, a dimension equal to only half a wave length of the light producing them. Lippmann solved the problem by coating glass with a suitable emulsion, and exposing it in a dark slide constructed to hold mercury. The glass side of the plate was turned to the light, and the sensitive film was backed up by the mercury which formed the reflecting surface. The evidence of his success lay in the facts that there was an obvious absence of pigmentary matter, the deposit being only grey silver, but that the colours of the original were reproduced as theory indicated by proper illumination and inspection, and that the colours changed by treating the film in any way that would alter the distance between the layers of silver, as, for example, by breathing on the plate and so slightly expanding the film. Perhaps the chief difficulty of this method is in ensuring that when finished the film shall be in exactly the same condition as during the exposure, or at least that the distances between the silver deposits in the finished plate shall exactly correspond with the distances between the nodes of the standing waves of the incident light. The chief drawback to the results is that they must be illuminated and viewed at suitable angles. Many workers improved the process in details, and some very excellent results have been obtained.

It still remained to actually demonstrate the existence of the laminæ of silver in the film. Dr. R. Neuhauss, Mr. E. Senior, and others afterwards, cut transverse sections of Lippmann films and obtained distinct proof of the presence of the laminæ, but by far the most complete and successful investigation of

these films has been published quite recently by Prof. S. R. Cajal of Madrid. As the resolution of the laminæ requires an objective of a numerical aperture equal to or greater than the greatest available, Cajal swelled his sections in water and so obtained excellent definition. He has photographed sections of all kinds, and analysed the effects by such methods as rubbing away the surface to distinguish between the effects of the superficial and the underlying parts. He confirms Zenker's theory exactly, except, perhaps, with regard to white. This he found was not due to the production and mixing of all colours or even complementary colours, but to simple reflection from a superficial deposit of silver; and in tinted whites or light colours he also found this superficial layer, but here it is partly transparent, and the interference colours produced by the laminæ below show through it.

Although attempts have been made, up to quite recently, to perfect the methods in which silver subchloride is the sensitive material, Lippmann's process may be regarded as the final result of all attempts to photograph colour directly. It is an exceedingly beautiful process to the experimentalist, but it has so many possibilities of error that it is very uncertain, and therefore unsuitable for general purposes as a method of photography in colours.

II

The Young-Helmholtz theory of colour vision supposes that the normal human eye is sensitive to only three fundamental colours; that is, that the points of sensitiveness of the retina, whatever they may be, are of three kinds. When white light falls upon the retina all three are excited to a definite (or equal) proportion, and when this proportion of excitation varies we become conscious of colour. Granting this, it follows that if the colour can be found that corresponds to each kind of sensitiveness, we shall have three colours that will, by their mixture, serve to imitate every possible colour, including, of course, black and white. These three fundamental colours have been determined from time to time by various investigators, and may be roughly described as red, green, and blue. We may then, for reproduction purposes, regard the light reflected from any object whatever, when illuminated in any manner

whatever, as consisting of a mixture of these three colours (or two or one of them), and by restricting the light that falls upon a sensitive plate to one of them at a time, a photograph can be made of each light-constituent reflected by the object. The photographs are themselves colourless, but they are colour records, and it only remains to bring together the three colours as indicated by the photographs to produce a picture that appears of exactly the same colours as the original—because it has exactly the same effect upon the retina. In this case no colour is produced by photography or by the photograph : the colours are pigments or dyes, and the photography merely locates them.

This is the principle of "three-colour" processes, and, speaking practically, all indirect colour photography comes under this description. It must not be thought that three-colour work is dependent upon the Young-Helmholtz theory of colour perception—it is founded rather upon the experimental facts that underlie that theory. The theory and three-colour processes are better regarded as two independent products of the same set of facts, and these facts will remain whatever fate awaits the colour-vision theory. Indeed the connection between this theory and three-colour photography may not be so intimate as it appears to some to be. The colours that represent the three sensations are fairly definite, and Colonel von Hübl maintains that the number of sets of three colours that will serve for three-colour work is indefinite. He arranges the spectrum tints in a circle with complementary colours diametrically opposite each other on a plan that would take too long to describe here, and states that the best three colours will be at the angles of an equilateral triangle drawn in the circle, and that the triangle may be in any position. At the same time he allows that practical considerations—chiefly the difficulty of getting a bright yellow by the mixing of pigments—obliges one to use the three colours which, if they do not exactly match the three primary sensation colours, approximate to them. Sir William Abney, who has done a great deal of work in this connection, and is a very successful producer of colour photographs, accepts absolutely the Young-Helmholtz theory of colour vision as his guide, and has redetermined the spectrum curves of the primary sensations. Mr. F. E. Ives, who has worked as a pioneer with very notable

success in many departments of colour photography, does practically the same, working according to Maxwell's curves. On the other hand it has been stated that the colour screens used by various workers do not always conform to their theories. It must be borne in mind, however, that the dyes and pigments used have to be selected from those that are available, and that the best of them are only more or less close approximations to what is really sought for. Thus the theories as to the selection of the colours are more diverse than the practice.

Having obtained the red, green, and blue records, there are two distinct methods by which the colours may be combined to form the picture. Each may be caused to give its appropriate colour separately, as by the use of a set of three optical lanterns, each giving one of the required colours (the photograph regulating its distribution and intensity), the three coloured images being superposed on the screen. The three colours are added together, light is added to light; the combined effect of all three is white and their absence is black. In the other method the three colour prints are superposed to form a single print or transparency. Here the combined effect of all three is black, their absence is white, and each colour subtracts whatever it can from the light—the same light that passes through all of them. In the first case the lights are added, and in the second the absorptions. The first is sometimes called the additive method and the second the subtractive method. The colours transmitted by each of the three prints in the second method must be the complementaries of those transmitted in the first case. Taking for example a red patch in the original, this will give a transparent or depositless place on the print that represents the redness of the original, which, by the triple lantern method, would give a red patch on the screen as required. But for printing or staining purposes this holds no colour, and so remains colourless. The prints that represent the greenness and the blueness of the original will be coloured at this part, the former by a colour that absorbs green and transmits red and blue, the latter by a colour that absorbs blue and transmits red and green. Thus the only colour that can get through the three superposed coloured images is the red, as required. In the additive method each image contributes one of the three colours, in the subtractive method each image subtracts or absorbs one of the three colours. These are the

general principles of three-colour photography in its two main sections.

Three-colour photography is practised commercially on a very large scale, and has been investigated and discoursed upon by a vast number of persons. A great many have dealt with the subject from a purely scientific point of view, while printers, ink-makers, and others look only at practical results. I propose therefore only to indicate the chief facts concerning its development, and to consider the most important processes that are in use at the present.

It seems that Clerk Maxwell was the first, in 1855, to suggest the principle of three-colour photography, but he used it as an illustration of the functions of the three systems of nerves according to Young's theory rather than a suggestion for practical photography. He says: "Let a plate of red glass be placed before the camera and an impression taken. The positive of this will be transparent wherever the red light has been abundant in the landscape and opaque where it has been wanting. Let it now be put in a magic lantern along with the red glass, and a red picture will be thrown on the screen. Let this operation be repeated with a green and a violet glass, and by means of three magic lanterns let the three images be superimposed on the screen . . . a complete copy of the landscape, as far as visible colour is concerned, will be thrown on the screen. The only apparent difference will be that the copy will be more subdued or less pure in tint than the original." Then he goes on to consider the eye in connection with colour vision. At the Royal Institution in 1861, Clerk Maxwell showed the experiment, using tanks of coloured liquids instead of coloured glasses, and showed the photograph of a coloured ribbon with three magic lanterns; but of course the colours were deficient because it was almost impossible at that time to photograph by red or green light.

Within the next few years others engaged themselves with the subject, but the most notable worker was Louis Ducos du Hauron, who, in 1869, published a small volume, entitled *Les Couleurs en Photographie: Solution du Problem.* He described the triple lantern "additive" method; a method of combining the three coloured images by means of mirrors; the production of prints by superposition of the coloured images—the "subtractive" method and a single-plate method—the three colours being

arranged in fine lines or otherwise on one plate. In the same year he showed some results at a meeting of the Société Française de Photographie. By a curious coincidence, at the same meeting, Charles Cros entered into great detail as to the various possible methods of trichromatic photography. But Cros appears to have contented himself with suggesting how others might succeed, while Du Hauron put his notions to the test of experiment. Moreover, it appears that Cros was wrong in his colours, recommending pale tints of red, yellow, and blue for the screens for getting the three negatives.

Work of this kind was very difficult because of the insensitiveness of the collodion plates then employed to green and especially to red light. It was not until 1873 that the sensitising effect of certain dyes upon photographic plates was discovered by Prof. H. W. Vogel. Now by this means plates can be made usefully sensitive even into the infra-red. The possibilities of special sensitising, and the introduction of gelatine dry plates about 1878, cleared away many difficulties that sorely hampered and might well have discouraged the earlier workers. From this time the development of three-colour photography was a matter of perfecting details rather than evolving new principles, and devising methods for converting laboratory experiments into commercial methods.

The additive method—the three coloured images being separately illuminated—was made into a really practical method by Mr. F. E. Ives, of Philadelphia. Mr. Ives first exhibited his apparatus in London in 1892, but four years before this he had demonstrated the capabilities of the process at the Franklin Institute in Philadelphia. In 1893 his "photo-chromoscope," afterwards called "Krōmskōp," was on the market. The apparatus that he devised for the purpose consisted of a camera for taking the three colour records, a triple lantern for projecting the picture on to the screen, and the photo-chromoscope. This last is a compact apparatus containing three coloured glasses, one for each colour record as required, and a system of mirrors, so that the three coloured images are seen superposed by looking in at the eye-piece. Shortly afterwards the apparatus was made stereoscopic. The reproductions as seen in this apparatus are remarkably realistic, and I do not think that any method has surpassed them. The one drawback is that an apparatus has to be used for seeing the pictures. Mr. Ives says

that he worked "in accordance with the Young-Helmholtz-Maxwell theory of colour vision." "Although the three fundamental colour sensations are red, green, and blue-violet, the three images of the triple photograph are not made through red, green, and blue-violet glasses, nor by the action of red, green, and blue-violet rays, but each by the joint action of all rays that have power to excite the respective fundamental colour sensations, . . . according to the measurements of Maxwell and Abney." Thus the colour screens used for taking the object each transmitted a large proportion of the spectrum. But for viewing or projecting the photographs Mr. Ives claimed to use colour screens that transmit only a narrow band of the spectrum, just that part in each case that will best excite the one sensation, and, as far as possible, that only. The disadvantage of narrow-band colour screens is that they transmit comparatively little light, and it has been stated that the screens used by Mr. Ives did not well conform to his theory. I have already referred to the uncertainty of these matters, but assuredly Mr. Ives was guided by the principles he professed, and he was remarkably successful.

The necessity for taking three separate negatives is obviously a circumstance to be avoided if possible, and the method of avoiding it was pointed out by Du Hauron in 1869. It appears that the only practicable method of making one plate suffice is to divide the surface of the plate among the three colours, using such small parts of the plate for each that when viewed in the usual way these parts merge into each other, as the fine detail of the impression of a copper or steel engraving does. The drawback to all such methods is the great loss of light. If any colour is represented by only one-third the area of the patch that stands for it, the area which might otherwise be all colour is two-thirds black. Thus two-thirds, more or less, of the light that would form the image in Ives' apparatus is lost in a one-plate process, and the picture is correspondingly duller unless the light is proportionately increased. This can be accomplished if the picture is in the form of a lantern slide, by using the same light in the lantern but reducing the diameter of the picture on the screen from 10 ft. to 6 ft. or less, or from 8 ft. to something under 5 ft.

The first successful methods of this kind were worked out independently by Dr. John Joly, of Dublin, and Mr. J. W.

McDonough, in America, from 1892 to about 1898. The later years of this period include attempts to make the process workable, so that the screens necessary might be manufactured in quantity, but in this they were not successful. The three colours were arranged regularly in lines, and were applied to the glass by means of a ruling pen, though other methods were tried afterwards. Dr. Joly followed Ives very nearly so far as his colours were concerned, except that he sought to get his colours to accord with the more recently determined sensation curves. He used two colour screens—a "taking screen" that was fixed in front of the plate while the exposure was being made, and a "viewing screen" which was put in front of the positive for seeing the picture, and might be bound up with it as a fixture if preferred. The lines were always so coarse as to be obtrusive.

Quite recently, after years of work, Mr. John H. Powrie, of Chicago, assisted by Miss Florence Warner, has so far perfected a triple-line method that he has been able to show many excellent examples. He has overcome the difficulty of making the fine coloured lines by discarding ruling methods altogether. He coats the glass with a suitable colloid made sensitive with potassium bichromate, and exposes this to light under a black-line screen that has lines twice the width of the spaces between them. The light makes the colloid insoluble in warm water, so that when "developed" like a carbon print, the coating is entirely dissolved away where it was protected by the black lines of the screen, and remains on the glass in fine lines corresponding to the screen spaces. The plate is put into a solution of a green dye; the colloid absorbs the dye, and thus the green lines are formed. The colloid is made quite insoluble to fix the dye. The plate is then coated again, and treated exactly as before; but care is taken that the black lines of the screen hide the green lines already produced, and a red dye is used. It remains to get the blue lines that shall exactly fill the spaces between the two sets of lines already obtained and without any overlapping of them. The plate is coated again, and this time exposed to light without the black line screen, but with its back to the light, so that the red and green lines on the plate prevent any light effect on the coating that overlies them and acts only upon the parts between. Warm water dissolves away the new colloid layer over the green and

red lines, leaving it exactly filling the spaces between them. The plate is put into a solution of a blue dye to stain the new lines. By this method the lines can be made more than twice as fine as by ruling (more than 600 to the inch), and the troubles of overlapping and of uncoloured gaps are entirely obviated. The method of using these plates, when they are issued to the public, will doubtless be similar to that of the Lumière "Autochrome" plates, described in the next paragraph. Their special advantages will be referred to later.

It may be here mentioned in passing that during the last twelve years it has been shown by many workers to be possible to get three colours that will serve more or less well by the use of prisms or diffraction gratings instead of dyes or pigments. But these methods do not appear to lend themselves kindly to practical work, even if no exception is taken to the principles upon which they are based.

Instead of arranging the three colours in lines, they may be disposed in small hexagon or square patches. These methods have been patented, but nothing practical has yet come of the idea. The third alternative is a random grain, and a method of doing this by means of starch granules, which was described by Messrs. Lumière, of Lyons, rather more than three years ago, has just been commercially perfected. Quantities of starch granules of approximately uniform size are stained respectively red, green, and blue, mixed as thoroughly as can be in such proportions as present a neutral grey to the eye, and dusted over a prepared plate so that they adhere in a single layer, which is then pressed or dusted with a black powder (or both) to fill up the small spaces between the granules. A protective waterproof varnish is applied, and on this is spread an orthochromatic emulsion, so that the plate is complete in itself—photographic plate and colour screen in one. It is exposed on the camera exactly as usual, except that the glass side of the plate is put towards the lens, so that the light has to pass through the layer of coloured starch granules before it affects the sensitive film. The plate is developed, and the resulting negative, instead of being fixed, has the metallic silver that constitutes the image dissolved away, and the remaining silver salt reduced to the metallic state, thus transforming the negative into a positive. When viewed as a transparency, the colours as well as the form of the original are seen. The preparation of

these plates must be regarded as a triumph of manufacturing skill. Some very excellent results have been obtained with them, but the colours are readily affected by error in their treatment. The "grain" of these plates is not so fine as one might suppose from the fact that starch granules are used, for it is apparently impossible to thoroughly mix the differently coloured granules. They occur on the plates in groups up to a dozen or more of one colour, and the groups are visible by a magnification much too low to show the individual granules.

A one-plate process such as that just described obviously must have the same dyes for taking the photograph, that is for dividing the colour of the original into the three fundamental colours, as for viewing the result, and this is a disadvantage. It is due to the wide permissible choice of colours and the non-critical comparison of the resulting colours with those of the original that the results are acceptable. These plates reproduce the colours of the spectrum very poorly. Presumably in the selection of dyes the best compromise has been made for such photography as the plates will generally be used for. It is practically impossible to multiply such colour photographs by exposing a new plate to light under a finished plate, because, as we have seen in the first plate, two-thirds of the light is lost, and the effect of making such a copy would be to lose two-thirds of the light passing through the first. Such a copy would, therefore, have about eight-ninths of its surface dark, reducing the light that would otherwise be available to about one-ninth, and it would be so dark as to be almost useless. Mr. Powrie has shown how it is possible to overcome the difficulty when using his plates, by fixing a mirror on each side of the printing-frame so that the light impinges on the plate from three directions, and then by suitably separating the two plates by a sheet of glass or celluloid every line in the upper plate—the picture—can be made to give a line of three times its width on the lower plate. So each of the three colours in the upper plate covers the whole surface of the lower plate, and no light is lost. By using light that corresponds to one colour only, it is possible by this means to get a record of that colour on an ordinary plate that is continuous—that is, that covers its whole surface instead of being as the original is, in lines that cover only one-third of its surface. Three separate continuous colour records, one for each colour, can thus be obtained from the original single

plate, and any three-colour process can be worked from these records.

The subtractive method, in which the three coloured prints are superposed, and each subtracts its quota from the light that passes through, was foreshadowed by Du Hauron and by Charles Cros. The production of transparencies in this way engaged the attention of Mr. Ives, and in 1893 he showed me a very fine example, perhaps 8 in. by 6 in. or larger. But it is to Mr. Sanger-Shepherd and his firm that we owe the establishment of this process, and the supply of the necessities for it, so that it can be worked by any one who wishes to do so. The usual three colour records are obtained; the one from the red screen is printed on a lantern transparency plate and the image is toned to a greenish blue colour, and the other two records are printed on bichromated gelatine films supported on celluloid, exposing through the celluloid. These, after development in warm water, are stained by suitable dyes, and then mounted on the greenish blue image, preferably by cementing them together with Canada balsam. One advantage of this method is that the three coloured images can be tentatively placed together, and if one colour is predominant a little of the dye can be washed out from that print, while if one is deficient it can be stained deeper. A somewhat similar method was introduced in 1895 under the name of "Pinatype" by Messrs. Meister, Lucius & Brüning. Three transparencies are prepared from the ordinary three negatives, and under each of these is exposed a sheet of bichromated gelatine. These gelatine prints are washed, and each is immersed in its appropriate dye solution. The dye is absorbed where the gelatine has not been acted on by light, but where the combined action of light and the bichromate has fully affected it, it is hardened and does not absorb the dye. These are called "print plates," for their function is to give up the dyes they have absorbed to a sheet or glass coated with a soft film of gelatine, which is pressed into optical contact with each "print plate" in turn. The "print plates" can be used repeatedly. Messrs. Sanger-Shepherd have perfected a somewhat similar method for making colour prints on paper, but their gelatine prints, which absorb the dye and then give it up to form the final picture, are developed in warm water and so form low reliefs. As "carbon" prints can be made in any colour, some of the firms that make carbon tissues have devised methods by

which three carbon prints are made of the required colours from the three colour record negatives and then superposed.

As any method by which the three coloured impressions can be superimposed on paper will give a three colour print, various printing-press methods are available, and some exceedingly fine work has been done by collotype printing, the printing surface being of hardened gelatine and inked up with printers' inks. But the process that is of all the most advantageous, especially where many impressions are wanted, consists in the preparation of three "half-tone" blocks, one corresponding to each of the three colour records, and making from these three superposed impressions in the three necessary colours. The greatest difficulty of these methods is in the getting of suitable inks, for they should not only be of the correct colour, but they (or at least two of them) should be transparent, and they should be permanent. The most suitable colouring matters are too fugitive, so theory has to be compromised, and as none are really transparent there is always a tendency for the colour last printed to predominate. In spite of these drawbacks very excellent work is done commercially by this process, but probably never without "fine etching"—that is, proof impressions from the blocks are compared critically with the original by persons who have been trained to appreciate colour and drawing; and where the tints are incorrect the alterations required are marked on the impressions, and the blocks are returned to the etcher, who works on the faulty part. In the best work this proofing and correction is repeated until the result is satisfactory. The "half-tone" block prints a series of dots equidistant from their centres and larger as the tone or shadow is deeper. In superposing the three impressions no attempt is made—indeed it would be practically impossible—to print the corresponding dots exactly over each other, and the result is that sometimes the dots are superposed and sometimes juxtaposed, according to chance. This might appear to lead to a mixture of the additive and subtractive effects, and as the colours for the one method must be the complementaries of those used in the other, it might be supposed that confusion would result. It is not so, however. Where only one ink is required, and where all three are required to their fullest extent to give black, the case is simple. Take the intermediate case of a grey produced by juxtaposition only of the three inks and in such a manner that the white paper

is completely covered. As each ink absorbs one of the three fundamental colours, we may describe the grey roughly as one-third black and two-thirds white. If now the three colours are superposed they will produce black, but only one-third of the area of the spot of white paper concerned will be covered, so that the result will be actually one-third black and two-thirds white—practically as before.

In all the processes so far considered the colour has been produced by light, or its distribution has been controlled by it. But there is a radically different method that has been in the minds of those interested in these matters for nearly thirty years, and latterly has been worked upon by many investigators with more or less, but on the whole gradually growing, success. The three necessary colours are put on the paper to begin with, and the light destroys or bleaches those that are not wanted. The method depends upon the fact that light can affect a substance only when it is absorbed, and therefore when a mixture of unstable coloured substances is exposed to coloured light, there is always a tendency for those substances that are of the same colour as the light to survive the longest, because they reflect more of the light than the others. The difficulties in working out such a method are many. The three dyes must be of the right colours, they must be about equally bleachable by white light, they must be readily bleached or the exposure would be too prolonged, and it is desirable that they shall be rendered more stable after the exposure. Dr. J. H. Smith of Zurich about a year ago put this method on a commercial footing and issued the paper ready for exposure beneath the coloured original under the name of "Uto" paper. The colours are made more sensitive by the addition of anethole, and after the exposure the print is soaked in benzene or acetone to remove the sensitiser. This paper gives surprisingly vivid reproductions of the colour of the original, but obviously the prints are not very stable to light.

Thus the present practical methods of colour photography are "three-colour" methods, and they do not aim at reproducing colour, but only at imitating it. If the imitation is perfect by daylight it will probably be faulty by artificial light, and a spectroscopic analysis of the two colours will at once show their differences. The perfection of the imitation depends upon the skill of the worker as well as upon the characteristics of the

method. The colour of the photograph is not impersonal evidence of the colour of the original; but the same qualification applies to the vast majority of observation records. This much, however, may be said in favour of three-colour processes—if a series of photographs is made by the same process and with the same materials, the discrepancies of colour would probably be more easy to trace than the random errors possible when the colouring is done entirely by hand. Moreover, any one who is accustomed to photographic manipulations and others with practice can work some of the processes, while it must be the comparatively few who can ever hope to become skilled in applying colours with the brush.

THE EFFECTS OF ENVIRONMENT AND NUTRITION UPON FERTILITY

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EXPERIENCED breeders of animals have seldom failed to recognise that the generative system is particularly susceptible to changed conditions of existence. Buffon long ago commented on the fact that the domestic animals are as a rule far more prolific than their wild representatives, and Darwin, who made the same observation, was disposed to ascribe the increased fertility of the former to a long habituation to a copious food supply without the labour of seeking for it. On the other hand, it is equally well known that wild animals when brought into captivity often become sterile, while there are numerous instances also of domestic animals failing to breed as a result of removal to a new environment. Such sterility, when it occurs, is not necessarily (or even generally) associated with disease or want of vigour, for, as Darwin observed, wild animals in confinement are not infrequently notoriously healthy and long-lived, and nevertheless fail consistently to produce young. There is no evidence that the reproductive organs are themselves diseased, yet they seem incapable of performing their natural functions. Moreover, in those cases in which wild animals in captivity have proved fertile, the capacity to breed is not necessarily inherited by their offspring, although, as a general rule, the fertility tends to increase in subsequent generations. Thus, it was a considerable time before the canary bird was fully fertile, but it eventually became so, whereas certain of the nearly related finches, while producing hybrids with the canary, only occasionally reproduce their own kind when kept in captivity. Other wild birds again, such as most members of the great families of ducks, pigeons, and fowls breed as readily in confinement as in their natural state. Similar differences occur in the various groups of mammals. For instance, bears breed less freely in the Zoological Gardens

than most other carnivores, although it is difficult to assign a reason for this fact. Furthermore, it was pointed out by Darwin that close confinement cannot be regarded as a sufficient explanation of infertility in such cases, since the semi-domesticated ferret, for example, breeds readily when kept in closely cramped hutches.

There can be no doubt that those environmented conditions which are conducive to the occurrence of "heat" or œstrus are generally also favourable to fertility, for although it is true that many animals which have never succeeded in producing offspring in captivity have been observed to experience œstrus and indulge in sexual intercourse, there can be no question that a prolonged or frequently recurring sexual season is usually associated with an increased capacity to bear young. The origin of the breeding season has been discussed in two papers by Mr. Walter Heape,[1] who lays considerable stress on the part played by nutritive influences, as shown especially by the effects of certain stimulating foods upon the generative functions of sheep. But it is none the less evident that nutrition is not the sole factor in determining the time for breeding, for, as Mr. Heape points out, its occurrence is to a great extent seasonal, and is governed both by external forces (*e.g.* climatic influences) consequent upon periodic change, and by internal forces dependent on the inherited capacity of the individual.

Some interesting observations made by Mr. Bles on various kinds of Amphibia seem to have a bearing upon this question.[2] This observer shows that axolotls, as well as certain species of frogs and newts, can only be induced to breed in captivity in the presence of particular environmented conditions. Mr. Bles found that by feeding them copiously in summer and allowing them to hibernate in winter, and afterwards suddenly transferring them to an aquarium stocked with growing plants and provided with running water or with suitable pond water, these animals could be induced to spawn within a few days. He draws the conclusion that the difficulty so often met with in inducing Amphibia to breed is not due to any toxic influence on the gonads resulting from close confinement, but should

[1] Heape, *Quart. Journ. Micr. Science*, vol. xliv. 1900; *Proc. Royal Soc.* B, vol. lxxvi. 1905.

[2] Bles, *Trans. Royal Soc. Edinburgh*, vol. xli. 1906.

rather be ascribed to the absence of the necessary external stimuli without which the generative organs of animals are incapable of discharging their functions. This view may also help to explain why some animals (*e.g.* insects) make their appearance in great numbers in one year and are comparatively scarce in another.

In those animals which, as a general rule, breed readily in a state of domestication or confinement, it is probable that nutrition plays the most important part in regulating the capacity to produce offspring. That an insufficient or markedly abnormal diet must affect this power is almost self-obvious. It is also clear that the effects of excessive nutriment are likewise prejudicial to the proper discharge of the reproductive functions. No better example could be given of the way in which over-feeding results in a condition of sterility than that afforded by the barren Shire mares which have been a noticeable feature at recent agricultural shows. Breeders of cows and sheep have learnt from long experience and at great cost the disastrous consequences of an over-nourishing diet upon the fertility of their stock. It would seem, however, that owing to the desire to excel in the showyard breeders of draught horses are falling continually into the old error. In the classes provided for barren Shire mares there are invariably to be found some of the finest specimens of the breed, so that those animals which appear best calculated to produce a superior class of foals are useless for stock-breeding purposes. Little or nothing is certainly known regarding the way in which excessive feeding checks the tendency to conceive, but this result may probably be ascribed to fatty degeneration in the organs of reproduction.

It is a somewhat remarkable fact that, although numerous experiments have been undertaken to determine the effects of different methods of treatment upon wool, meat, or milk production, no systematic attempt had been made until quite recently to deal with the factors which influence fertility in livestock. A few years ago, however, the Royal Agricultural Society instituted an inquiry into the causes of barrenness and abortion among different breeds of sheep in the south of England. The investigation was conducted by Mr. Heape, whose report was subsequently published in the *Journal* of the Society.[1]

[1] Heape, "Abortion, Barrenness, and Fertility in Sheep," *Jour. Royal Agric. Soc.* vol. x. 1899.

In this report it is shown that in the season 1899 the proportion of ewes which failed to breed or which aborted their lambs was 6·76 per cent., and that the number which produced twins was about 30 per cent. The most fertile of all the breeds was the Wensleydale, in which six flocks consisting of a total of 319 ewes produced a percentage of 177·43 lambs. The effects of locality are also discussed, and there is an accumulation of evidence which seems to indicate that the character of the district is not without influence on the fertility of the breed. Thus the records show that whereas the sheep belonging to the Lincoln variety in Yorkshire produced an average of 47·57 per cent. of twins, those in the home county had only 25·11 per cent., while those in neighbouring counties produced 33·78 per cent. With other breeds the variation in the fertility in different districts, while quite noticeable, was not so pronounced as in the Lincoln sheep.

The report shows, further, that the fertility of a flock depends greatly upon its management, that the quality and quantity of the food supplied affect the condition of the sheep and so influence their capacity to breed, that some seasons are far more favourable to fertility than others, and that sheep-stained pasture (*i.e.* pasture on which sheep have recently been kept for some little time previously) is often prejudicial to breeding stock.

As a result of a recent investigation upon the reproductive processes in sheep, it has been shown that (in the breeds investigated) the normal percentage of Graafian follicles discharging their ova at any single "heat" period does not appreciably exceed the usual percentage of births at the lambing season. It would seem, therefore, that a comparative scarcity of twins at lambing time is almost certainly directly correlated with an abnormally small number of ripe follicles in the ovary at tupping time (*i.e.* during the breeding season). An unusually low percentage of twins is closely associated with barrenness. This fact is generally recognised by flockmasters, and Mr. Heape's statistics prove it very clearly. And since habitually (*i.e.* constitutionally) barren ewes are a rarity, there can be little doubt that barrenness is due normally to the same cause operating on a more exaggerated scale—*i.e.* to the absence or great scarcity of Graafian follicles available for ovulation during the tupping season.[1]

[1] Marshall, *Phil. Trans.* B. vol. cxcvi. 1903.

Scarcity of ripe follicles at tupping time must clearly result either from retardation in follicular development or from an unusual amount of follicular degeneration, either recently or at some previous period in the animal's lifetime. Degeneration of follicles is by no means uncommon in the ovaries of sheep, and appears to be most frequent in those which have attained to from one-eighth to one-half the dimensions of the mature follicle. It may set in, however, at practically any stage of development. The follicle, instead of continuing to grow, undergoes a series of retrogressive changes, which result in the shrivelling up of the ovum and the ultimate absorption of the entire contents of the follicle. There can scarcely be any doubt that the degeneration is usually the result of an insufficiency of stimulating power at the disposal of the ewe.

That scarcity of mature follicles in sheep's ovaries at tupping time may be due to retardation of growth is a conclusion that is based on inference rather than on direct observation, for little is known concerning the rate of development of the Graafian follicle. There is every reason for believing, however, that the process of ripening can be very largely influenced both by insufficiency of food supply on the one hand, and by artificial stimulation on the other.

This fact has been perfectly well realised for years past by certain individual flockmasters, who have consistently practised the methods of flushing or artificially stimulating their sheep by means of an extra supply of special food at the approach of the breeding season. It is somewhat surprising, however, that no precise records of the effects of flushing upon fertility had been collected until quite recently, when the Highland and Agricultural Society of Scotland undertook an inquiry upon this subject. The absence of published information may perhaps explain the prevalent ignorance of the results of flushing among many sheep-breeders who have never adopted it.

In a preliminary report upon the Highland Society's investigation[1] containing the lambing statistics for various Scottish breeds in the year 1905, it is shown that the percentage of lambs born was, as a rule, largest among flocks which had been subjected to a process of artificial stimulation. The method adopted was to feed the ewes upon turnips, oats, dried grains, maize, or other artificial food at the tupping time and for about

[1] Marshall, *Proc. Royal Soc.* B, vol. lxxvii. 1905.

three weeks previously, while maintaining them upon grass only during the greater part of the year. Some flocks, however, received a limited quantity of additional food (turnips, etc.) during pregnancy, and especially during the latter part. The statistics show that in the flocks which were treated in this way the percentage of lambs per ewes[1] was considerably in excess of the average percentage for flocks which received no special treatment, while the percentage of barren ewes was generally appreciably less. In some cases the number of lambs per ewes[1] in the flushed flocks was nearly 200 per cent. Among flocks of the same breeds (Border Leicester or half-bred Border Leicester) which received no sort of special treatment, the average proportion of lambs per ewes[1] was between 150 and 160 per cent., while flocks which were placed upon superior pasture at the approach of the breeding season (without being otherwise specially fed) generally produced a slightly larger percentage of lambs (about 160 per cent.).

It may be of some interest to describe more precisely the method of treatment adopted for certain of the flushed flocks in which a relatively large number of twin lambs were produced.

In one of these the ewes (which were half-bred Border Leicester by Cheviot) were fed upon grass only during the summer previous to tupping. For three weeks (during tupping, beginning of October) they were allowed a full supply of turnips upon grass. Between tupping and lambing (five months) they were given a mixture of dried grains and turnips, and lamb food for three weeks before lambing. The rams (which belonged to the pure Border Leicester breed) were fed upon bruised oats during tupping. The percentage of lambs per ewes[1] was 191·5. One ewe had four lambs and 12·5 per cent. had triplets. None of the ewes were barren and none aborted.

In a second experiment the ewes (which were also half-bred), after being kept upon grass during the summer, were supplied with Bombay cake, bruised barley, and a little linseed, as well as turnips and cabbages during the tupping season. Some turnips were given during pregnancy. The rams (Border Leicester and Oxford Down) were treated in the same way. The percentage of lambs per ewes[1] was 193·75. None of the ewes aborted and none were barren. Triplets were produced in 13·5 per cent. of the ewes.

[1] That is to say, the number of lambs per 100 ewes.

In a third case the ewes (half-bred) were placed upon superior pasture at tupping, and from that time onwards until lambing they were supplied with hay and turnips. Previous to tupping they were fed upon grass alone. The rams (Border Leicester, Oxford Down, and Cheviot) were treated similarly to the ewes before and during tupping. The percentage of lambs per ewes[1] was as high as 196. Out of 184 ewes 23 had triplets. Two ewes aborted and one was barren.

In another experiment 60 ewes were placed upon rape and seeds at tupping time. Of these, 54 produced either twins or triplets at the following lambing, the proportion far exceeding that in the other sheep which were upon the same farm but not similarly treated.

The Highland Society's investigation is still in progress, and a full report will not be issued until next year. In the meantime it may be stated that further experiments fully confirm the conclusion that stimulation of the generative organs of sheep by a system of special feeding at the beginning of the breeding season results in an increased crop of lambs at the following lambing season. The twins appear almost invariably to have been born early during lambing, thus showing that the reproductive activity of the ewes is usually greatest at the beginning of the breeding season.

There is abundant evidence also that flushing tends to hasten the time for breeding. It has been shown recently that the condition of "heat" in animals is probably brought about through the action of an internal secretion or chemical excitant elaborated by the ovaries.[2] It would seem, therefore, that the artificial feeding exercises a stimulating influence over the secretory activity of the ovaries, while at the same time promoting the more rapid growth and maturation of the follicles, and causing a larger number to discharge their ova at the earlier "heat" periods of the breeding season.

It has so far proved more difficult to obtain precise information regarding the effects of flushing in one season upon the fertility of the sheep in after-years. The more usual experience of those flockmasters who have practised flushing appears to be that this process is not in any way detrimental unless it is over-

[1] That is to say, the number of lambs per 100 ewes.

[2] Marshall and Jolly, *Phil. Trans.* B, vol. cxcviii. 1905. Cf. also Knauer, *Arch. f. Gynäk.* vol. lx. 1899; and Halban, *S.B. Akad. Wiss.* Wien, vol. cx. 1901.

done. If the artificial feeding is excessive, and the sheep are made to depend for the rest of the year (*i.e.* during gestation and afterwards) upon nothing better than sustenance diet, one might reasonably expect the ewes to deteriorate, and their subsequent fertility to be impaired. It is apparently for such a reason as this that some breeders, especially in England, regard the practice of flushing as altogether to be deprecated. In this connection it should be mentioned that there is some evidence for the belief that if sheep are flushed in one year, the process must be repeated in the next, and that if this practice is not adopted, the ewes tend to be less fertile than if they had never been flushed at all.

On the other hand, certain of the reports show that sheep which produce twins one year, in a large proportion of cases bear twins also in the year following. This appears to occur irrespectively of flushing. It would seem, therefore, that an increased degree of fertility is a characteristic of certain particular ewes.

Before concluding this brief summary of recent investigation upon certain of the factors which control fertility, I may take this opportunity of urging the importance of further inquiry in the interests of the livestock industry. In these days, when much is heard of agricultural depression, it is not always realised that the breeding of domestic animals is one of the staple industries of the country. The prominent position which British horses, British sheep, and British cattle still hold in the livestock markets of the world is, perhaps, the most hopeful indication for the future of British agriculture. It is a sufficiently remarkable fact that, excepting for the Holstein cattle, the Percheron horses, and the Merino sheep, all the prominent breeds of livestock throughout the world have their foundation in animals of British ancestry.

Even the Percheron horses are not the equals of the English Shires for stamina and power. Nearly every good horse on the Continent and in America is derived from British stock. The famous American trotters are descended from English hackneys. At the international conference of sheep-breeders which recently met at Ipswich, great stress was laid upon the high favour in which British sheep are always held by the great cosmopolitan buyers. The livestock export from Great Britain goes on increasing year by year, and last year was phenomenal,

reaching a grand total value of a million and three-quarter pounds.

And yet, despite its comparative prosperity, it is very evident that the breeding industry suffers annually from no inappreciable loss. The prevalent sterility among the better class of Shire mares has already been alluded to, while incapacity to breed is perhaps still commoner among Thoroughbreds, for the Royal Commission on Horse-Breeding showed that no less than 40 per cent. of the country's thoroughbred mares fail to have foals each year. Among cattle the annual loss from sterility has been estimated at 15 per cent., while it is shown in the report of the Royal Agricultural Society on fertility in English sheep for the year 1899 that the proportion of ewes which failed to breed was over $6\frac{1}{2}$ per cent. In view of the facts of which these are only examples, it is sufficiently obvious, as Mr. Heape has pointed out, that any means by which sterility can be reduced and the capacity to bear young increased must be possessed of great commercial value. And this result can only be attaiend by continuous scientific investigation and the introduction of scientific method into all the problems of practical breeding.

Mr. Heape, in his work on *The Breeding Industry: Its Value to the Country and its Needs*, has shown from statistical evidence that the amount of money invested in livestock in this country must be computed at scarcely less than £450,000,000. Adding to this the capital spent on buildings, land, vehicles, and various accessories, the total becomes still more gigantic. And yet what Mr. Bateson said at the Cambridge meeting of the British Association three years ago is still almost true: "Breeding is the greatest industry to which science has never yet been applied." It cannot be doubted that the introduction of rigorous scientific method into the breeder's industry will be attended by immense advantage, just as it has proved invaluable to other industries.

WORK UNDER PRESSURE AND IN GREAT HEAT[1]

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The development in all directions of engineering and manufacturing work is constantly bringing man into new and unaccustomed relations with his environment. In consequence of this, his working efficiency may be reduced very greatly, and his health, or life itself, may be endangered. The question of how to carry on work safely and efficiently under an unwonted environment is thus one which occurs in many forms to those who are engaged in our branch of science. In the present address I wish to glance shortly at several problems of industrial hygiene, presented by work beneath water or beneath the ground, and at some recent attempts at their investigation and practical solution.

I shall refer first to work in deep water under the sea. In consequence of the difficulties and dangers connected with the work of divers on the sea-bottom, the British Admiralty two years ago appointed a Committee to investigate the subject, with myself as the physiological member. The experiments carried out by this Committee, and at the Lister Institute, London, in close connection with it, are now completed; and I propose to give some account of the results, which, like many other British investigations on questions of hygiene, are hidden under the somewhat forbidding form of an official blue-book.[2]

Let me remind you that the ordinary diving dress consists of a copper helmet screwed to a corselet, the latter being in its turn connected water-tight to a stout waterproof dress covering every part of the body except the hands, which project through elastic cuffs. Air is supplied through a non-return valve on the helmet from a flexible pipe connected with an air-pump on a boat or

[1] An address delivered at the General Meeting of the International Congress of Hygiene, Berlin, September 26th, 1907.

[2] *Report to the Admiralty on the Conditions of Deep Diving*, 1907.

ship: the air escapes through an adjustable spring valve at the side of the helmet. The arrangement is thus such that the pressure of the helmet air breathed by the diver is always equal to, or slightly greater than, the pressure of the water at the valve outlet. At a depth of 10 metres (33 ft.) the diver is therefore breathing air at an excess pressure of 1 atmosphere, or at an absolute pressure of 2 atmospheres; and every additional 10 metres will add another atmosphere to the pressure.

Provided that about 50 to 100 litres of air per minute are supplied to the diver, and that the outlet valve of his helmet is properly adjusted, he can work quite comfortably at depths up to about 20 metres. Beyond this depth, however, he usually feels increasing discomfort and difficulty in working; so that at 40 or 50 metres work becomes extremely difficult. This difficulty has hitherto been ascribed to the pressure: its real cause was one of the first points which we investigated. We found that the discomfort of the diver was associated with laboured or dyspnœic breathing; and this fact, in connection with the results of recent experiments on the normal regulation of breathing, suggested the true explanation.

In a paper published two years ago by Mr. Priestley and myself,[1] it was shown that under normal conditions the breathing is always regulated in such a way as to keep the partial pressure of the carbon dioxide in the air of the lung alveoli almost exactly constant. This fact was established by analysing samples of air from the lung alveoli in man. To obtain a sample all that is necessary is to make a sudden deep expiration (during perfectly natural breathing) through a long piece of tubing of wide bore, and at once withdraw into a gas-analysis apparatus a portion of the air left in this tube at the end of expiration. The deep expiration washes out all the more or less pure air contained in the air-passages and tube before the deep expiration, and leaves the tube full of pure alveolar air. This pure alveolar air contains for each individual an almost astoundingly constant percentage of CO_2 if the barometric pressure is constant. If the barometric pressure varies, the percentage of CO_2 varies inversely as the barometric pressure, so that the partial pressure of CO_2 remains constant. For instance, we found in ourselves that the mean percentage

[1] *Journal of Physiology*, vol. xxxii. p. 225, 1905.

of CO_2 in our alveolar air was 6·01 at normal pressure, and 3·53 in compressed air at 1·7 atmospheres absolute pressure. The corresponding partial pressure of CO_2 in the alveolar air was 5·68 per cent. of an atmosphere, or 43 mm. of mercury, during respiration at normal pressure, and exactly the same in the compressed air. Thus the respiratory centre normally responds only to variations in the partial pressure of CO_2 in the blood which irrigates it. To variations in the partial pressure of oxygen it is within very wide limits absolutely indifferent. Only when the partial pressure of oxygen in the air inspired falls below about two-thirds of the normal does the respiratory centre begin to respond to want of oxygen. Quite recent experiments by Hill and Greenwood at high pressures in air, and by Boycott and myself at low pressures in a mixture of oxygen and air, have shown that at an absolute pressure of 6 atmospheres the alveolar CO_2 percentage was 0·9, and at 0·4 atmospheres it was 15; while at normal pressure it was about 5·5 with the same individuals. The partial pressure of CO_2 (*i.e.* the percentage in the moist alveolar air multiplied by the barometric pressure) remained, however, quite constant.

If CO_2 is present in the air inspired, the effect is to make the breathing deeper, and finally also more frequent; unless, however, the pressure of CO_2 in the inspired air begins to approach the normal alveolar CO_2 pressure, there is very little change in the alveolar CO_2 pressure, compensation being produced very easily.

How, now, does this apply to the case of the diver? On account of the work involved in pumping, a diver has to content himself with a minimum supply of air. Let us suppose that when he is just under water he has sufficient air to prevent the CO_2 percentage in the helmet air from rising beyond 3 while he is at work. This will keep him fairly comfortable. If he now goes down 10 metres, the air supply being the same, the percentage of CO_2 in the helmet air will also remain the same. As, however, the pressure is now 2 atmospheres, his normal alveolar CO_2 percentage will be 2·8 instead of 5·6. It will, however, be quite impossible for him to maintain this percentage of CO_2 in his alveoli, since during work the percentage in the inspired air itself is 3. He will thus suffer from severe dyspnœa. A very little consideration will show that the diver must have twice as much air at 10 metres if he is to be as comfortable as he

was at surface; and at whatever depth he may be his minimum air supply must be increased in proportion to the increase in the absolute air pressure. In other words, the minimum *volume* of air supplied to him, measured at the pressure he is under, must always remain the same.

To cut a long story short, we found that as soon as this condition was realised, as proved by numerous analyses of air from the helmet, the discomfort and loss of working power in deep water disappeared. Lieutenant Damant and Gunner Catto, the two officers who carried out most of the experiments in deep water, and who reached the greatest depth hitherto definitely recorded, were as free from respiratory distress at 64 metres (210 ft.) as at 1 metre. They could also reach this depth easily within two minutes, which showed the extraordinary fallacy in the time-honoured tradition that a diver should always descend slowly, so as to accustom himself by degrees to the change of pressure.

By guarding against excessive increase of CO_2 pressure in the air breathed by a diver, we not only increase greatly his working efficiency and comfort, but also obviate a serious danger. It not infrequently happens that a diver, particularly if he is somewhat unskilled, becomes unconscious or stupefied by the effects of CO_2. The consequences of this may easily be fatal, as it is very dangerous to draw a man up rapidly from a great depth if he has been down for any time; and also dangerous to leave an unconscious man on the bottom.

In connection with the effects of CO_2 in a diver's helmet, I should like to say something as to the presence of CO_2 and other impurities in the air of mines. It is well known that an excess of CO_2 and corresponding deficiency of oxygen is commonly met with in the air of mines, and that certain kinds of mining work are very unhealthy—particularly the mining of some of the more valuable metals, such as gold, tin, silver, copper, and lead. On account of the high death-rate and large amount of illness among the tin-miners of Cornwall in England, I was asked in 1902 by the British Government to investigate the ventilation of the mines there. It was known from the results of an earlier inquiry,[1] confirmed by my own analyses, that it is easy enough to find many working places in these mines where the proportion of CO_2 rises to as much as 50 volumes per

[1] *Report of the Royal Commission on Metalliferous Mines*, 1864.

10,000 of air, or higher; and much stress had been laid on the gaseous impurities of the air as explaining the ill-health of the miners. The physiological data already mentioned prove, however, that although an actual rise of ½ or 1 per cent. in the alveolar CO_2 pressure would have most violent physiological effects, no such rise actually occurs when air containing ½ or 1 per cent. of CO_2 is breathed. The only effect is that the breathing becomes very slightly deeper, the difference being subjectively quite inappreciable. Less than 1 per cent. of CO_2, or 100 volumes per 10,000, is therefore of no importance in air at ordinary pressure, provided no other harmful inpurity is present. Except in exceptional cases—for instance, just after blasting—there was no evidence of any other harmful gaseous impurity in the mine air; and by far the greater part of the CO_2 was found to arise from the slow oxidation of mineral matter such as iron pyrites (FeS_2), with consequent liberation of CO_2 from carbonates by the sulphuric acid formed.

What, then, was the cause of the ill-health of the Cornish miners? Further examination[1] into the facts disclosed two causes. The first was that certain of the mines were badly infected with ankylostomiasis, which, as has so often been the case during the last hundred years, had not been recognised, and which was soon brought under control by suitable measures. The second, and by far the more serious, cause was the fact that dust raised locally by drilling and blasting granite, quartz, and other hard stone was being inhaled by the miners and causing injury to their lungs which produced a marked predisposition to tubercular phthisis. The increased death-rate among the miners was due entirely to lung disease, chiefly tubercular phthisis. During middle life, for instance (age thirty-five to forty-five), the death-rate from lung disease was 33 per 1,000 among Cornish miners, as compared with 3·4 per 1,000 among coal and iron miners; and from all other causes 5·8 per 1,000 among Cornish miners, and 6·5 per 1,000 among coal and iron miners. An investigation of the working history of each man who had died in one of the mining districts during a period of three years revealed the fact that the extra deaths—at any rate during middle life—were confined almost entirely to men who had been engaged either locally or

[1] *Report on an Outbreak of Ankylostomiasis in Cornish Mines;* and *Report on the Health of Cornish Miners*, Parliamentary Papers, 1902 and 1904.

abroad in the dustiest work—namely, the management of machine drills worked by compressed air. By the use of water jets or other means, which I need not specify in detail, the inhalation of stone-dust from these drills and from blasting can be entirely prevented; and legislation rendering effective means compulsory was carried through at once with the full support of the management of the mines.

The accompanying tables show some of the Cornish statistics:

TABLE I

Annual Deaths per 1,000 *living at each age*

	Ages					
	15–20	20–25	25–35	35–45	45–55	55–65
All miners (Cornwall):						
Lung diseases	0·7	2·7	17·3	33·2	32·2	42·6
All other causes... ...	1·0	3·1	3·6	5·8	12·4	27·9
Coal miners (England):						
Lung diseases	0·9	2·0	2·1	3·5	7·8	18·7
All other causes	2·9	3·6	4·2	6·5	11·6	25.1
Ironstone miners (England):						
Lung diseases	1·6	1·5	2·1	3·2	6·5	13·0
All other causes	1·8	3·1	3·8	5·0	10·6	20·3
All occupied males (England):						
Lung diseases	0·95	2·7	3·7	5·9	8·6	13·0
All other causes	1·6	2·4	3·6	6·5	12·9	20·7

TABLE II

Deaths of all men who had ever worked Machine Drills, and who died in Redruth District, Cornwall, 1900-2

	Ages					Total.	Mean Age at Death.	Mean Duration of Machine Drill Work.
	15–25	25–35	35–45	45–55	55–65			
Lung diseases	3	51	54	22	3	133[1]	37·2	7·0 years
All other causes	2	4	1	2	0	9	—	—

It is a remarkable fact that while the inhalation of dust from hard stone is extremely dangerous when habitually inhaled, the

[1] Of these, 122 were returned as phthisis.

dust from coal, or soft stone, and many other materials, has no such effect, at least in moderate quantities. An average English coal-miner inhales very large amounts of coal-dust; but coal-mining is one of the healthiest of all occupations, in spite of absence of light, exposure to extremes of temperature, and the inhalation of air which is, chemically speaking, far from pure. It just happens that the ordinary impurities—moderate excess of CO_2, CH_4, dust from coal and shale, and deficiency of oxygen—matter comparatively little from the health point of view, whereas dust from hard stone matters a great deal.

I must now return to deep diving. The most formidable danger presented by this occupation occurs only on the ascent of a diver to surface. It has been known for long that divers and other workers in compressed air are subject on their return to surface to a variety of serious symptoms—in mild cases only pains in the limbs or elsewhere (usually known among English workers in compressed air as "bends"); in more serious cases paralysis, either temporary or permanent, particularly of the legs and bladder; or, finally, symptoms of asphyxia, which may prove rapidly fatal. The classical experiments of Paul Bert[1] proved, thirty years ago, that all these symptoms are due to liberation of gas-bubbles in the blood or elsewhere within the body; and considerable further light has been thrown on this subject by more recent work, including particularly that of Catsaras, von Schrötter,[2] and Hill. It was on the prevention, rather than on the pathology, of these symptoms, known collectively as caisson disease, that the Admiralty Committee concentrated its attention. The blood and body tissues become saturated with gaseous nitrogen in accordance with Dalton's Law during exposure to compressed air. On rapid decompression this gas liberates itself in the blood as bubbles, which cause local or general blocking of the circulation, with corresponding symptoms. Paul Bert showed on animals that in order to avoid this condition decompression must be slow; but the question, How slow? had not been satisfactorily answered in the case, at least, of man. The nearest attempt at

[1] *La Pression Barométrique*, 1878.

[2] Heller, Mager, and von Schrötter, *Die Luftdruckerkrankungen*, Vienna, 1900; von Schrötter, *Der Saurerstoff in der Prophylaxie und Therapie der Luftdruckerkrankungen*, 2nd ed., Berlin, 1906.

an answer was that of von Schrötter and his colleagues, based in part on theoretical considerations suggested by Zuntz, and evidently to a large extent correct. In many points, however, it seemed to us that von Schrötter's conclusions were open to criticism. Practical experience, for instance, seemed to show that it takes far longer than he believed for the human body to become saturated with nitrogen in compressed air, and a correspondingly longer time to become desaturated. Similar criticisms applied to the conclusions of Hill and his colleagues on this subject.[1]

It was evidently necessary to make further experiments, and these were rendered possible in England by the gift to the Lister Institute by Dr. Ludwig Mond, F.R.S., of a large experimental steel chamber capable of comfortably taking a number of animals or several men. In this the experiments were carried out by Dr. A. E. Boycott, of the Lister Institute, Fellow of Brasenose College, Oxford, and Lieutenant Damant, the naval officer who, as already mentioned, was also engaged in experiments on himself and others in deep water at sea. For the experiments on animals goats were selected, as we were convinced from the outset that small animals, in consequence of their rapid circulation, were useless for our purpose. Indeed, very small animals showed no symptoms whatsoever after exposures from which rapid decompression killed goats with certainty, and *a fortiori* would have killed men. With long exposures to high pressures the risks to be guarded against on decompression are undoubtedly still greater in men than in goats.

Several hundred decompressions of goats, men, and other animals have been carried out during 1906 and 1907 by Boycott and Damant. In the time available I cannot, however, give more than an outline of some of the results.

In the first place it was found that, with equal conditions as regards decompression, the symptoms observed in goats increased in danger and severity as the duration of exposure increased up to at least two hours or perhaps somewhat more. This is illustrated in Table III., showing some of the results:

[1] *Journal of Hygiene*, vol. iii. p. 436, 1903; *Proceedings of the Royal Society*, vol. lxx. p. 455, 1903; vol. lxxvii. p. 442, 1906; vol. lxxix. p. 21, 1907.

TABLE III

Absolute Pressure 4 Atmospheres

Exposure in Minutes.	Decompression in Minutes.	Number of Goats.	Cases of "Bends."	Severe Symptoms.
15	1	15	1	0
30	1	15	3	0
60	1	14	4	0
120	1	10	2	4
60	10 (uniform)	11	3	1
120	10 „	11	4	1
240	10 „	11	4	1
480	10 „	11	3	2

Allowing, therefore, for the difference between goats and men in the respiratory exchange per unit of body weight, and consequent rate of circulation, it would take about four hours for a man's body to become for practical purposes saturated with nitrogen in compressed air. This conclusion harmonises with the experience of workers in compressed air. Parts in which the circulation is rapid are certainly saturated in a small fraction of this time, as indeed has been shown experimentally by Hill by determining the amount of free nitrogen in urine secreted during rapid diuresis.[1] We think, however, that von Schrötter, who calculated that saturation is nearly reached in man within about twenty minutes, has at any rate made a great *practical* underestimate, both of the time needed for saturation and that needed for desaturation. In making his calculation, he has treated the body as if the circulation through all parts were the same, whereas it differs very greatly in different parts. From the point of view of caisson disease, the quickly saturating parts cause little danger (except with almost instantaneous decompression from very high pressure), as is shown both by the practical experience of men working in compressed air, and by the fact that it is extremely difficult to produce any symptoms in small animals with a rapid circulation rate. It is thus the slowly saturating parts of the body which are of most practical importance. Another source of error is that, as was shown by Dr. Vernon,[2] of Oxford, in connection with our experiments, fat

[1] *Proceedings of the Royal Society*, vol. lxxix. p. 366, 1907.
[2] *Ibid.*

takes up about six times as much free nitrogen as does blood. The body fat thus forms a very large depôt of nitrogen, which greatly increases the time needed for saturation. On sudden decompression of an animal saturated with compressed air the fat becomes blown out with small gas-bubbles.

We are in complete agreement with von Schrötter and Zuntz as to the general form which the saturation curve of any part of the body must of necessity take, assuming the rate of circulation to remain constant (see fig. 1). For instance, a part which takes one hour to become half-saturated will take two hours to become three-fourths saturated, and three hours to become seven-eighths saturated. During desaturation on decompres-

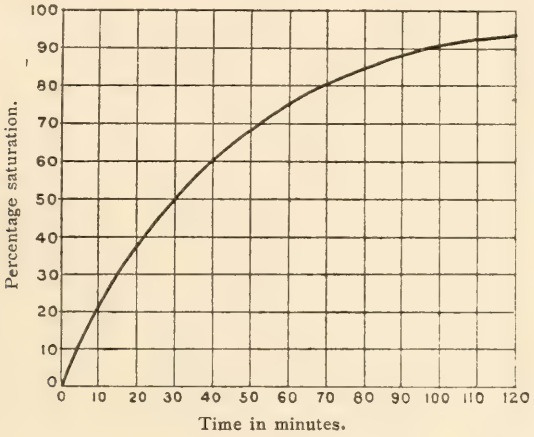


FIG. 1.—Curve showing approximate rate of saturation of parts of the body with an average rate of circulation and percentage of fat.

sion, if no bubbles have formed to disturb the process, the desaturation curve will be exactly the same.

I now come to another point, as to which we have been led to new and important conclusions. Practical experience of work in compressed air shows that even with very rapid decompression no symptoms of caisson disease ever occur with an absolute pressure of less than 2 atmospheres, and that symptoms are very rare and slight until the pressure rises beyond 2·3 atmospheres, or 19 lb. per square inch. This we found to be true also for goats. Now if it is possible to decompress rapidly and with safety from 2 atmospheres, or a little more, to 1 atmosphere, it seemed likely that it would be possible to decompress with

equal safety from 4 atmospheres to 2, or from 6 to 3, since the volume of gas tending to be liberated would be the same in each case. Experiment showed that this was the case, and that the danger of rapid decompression depends, not on the absolute difference between the initial and final pressure, but on the proportion between the two pressures. If this proportion is only 2 or 2·3 to 1, the decompression is safe; if, on the other hand, the proportion is 3 or 4 to 1, the decompression is dangerous. This is illustrated by the experiments in Table IV.

TABLE IV

Absolute Pressure in Atmospheres.	Exposure in Minutes.	Fall of Pressure in Atmospheres.	Relative Reduction of Pressure.	Duration of Decompression in Minutes.	Number of Goats.	Cases of "Bends."	Severe Symptoms.	Death.
6	180	3·4	2·3 to 1	1½	10	0	0	0
4·4	180	3·4	4·4 ,, 1	4	10	3	3	2
4	120	3·4	6·7 ,, 1	6	3	1	1	1
3·6	120	3·0	6 ,, 1	6	4	0	3	0
4	120	3·0	4 ,, 1	1	10	2	4	0

It will be seen that a rapid drop from 6 to 2·6 atmospheres produced no symptoms at all, the fall of pressure being 3·4 atmospheres, and the relation of the higher to the lower pressure being 2·3 to 1. With the same animals decompression from 4·4 atmospheres to 1 produced disastrous effects, the fall of pressure being exactly the same as before, but the relation of the higher to the lower pressure being now 4·4 to 1.

The method hitherto recommended for bringing men safely out of compressed air has been to decompress at a slow and uniform rate. But calculation on the principle already referred to shows that however slow this uniform decompression may be, the difference in partial pressure between the nitrogen dissolved in the tissues and the external air pressure will go on increasing during the decompression. Still more will the proportional difference between the two pressures increase. At the end of the decompression, therefore, the danger, if any, will be at a maximum; whereas during the first half, or more, of decompression time is simply being wasted, or much worse than wasted, if saturation of the body was incomplete, as is nearly always the case in diving. All our experiments confirmed this theoretical deduction.

These considerations led us to introduce a new method—that of decompression in graduated stages. The principle of this method is that the diver or worker in compressed air is brought rapidly to half the absolute pressure (or a little further if his tissues are not saturated), stopped there for a time, then decompressed a little further after sufficient time has elapsed to allow the maximum nitrogen pressure in his tissues to become not more than twice the nitrogen pressure of the air at the lower stage. He is then brought on by further stages on the same principle until he reaches atmospheric pressure. For the difference between the stages a pressure of 0·3 atmosphere was selected, corresponding to 10 ft. (or 3 metres) of sea water. The diver's progress is, of course, controlled by signal from surface, according to the indications of the pressure-gauge on the pump. The proper stoppages, after stays at different depths and for different periods of time, have been carefully calculated and put into the form of a table, which is now in use in the British Navy. A portion of this table is shown in Table V.

TABLE V

Portion of Diving Table for British Navy

Depth.		Total Pressure in Atmospheres.	Time from Surface to beginning of Ascent.	Depth and Duration in Minutes of Stoppages during Ascent.				Total Time for Ascent in Minutes.
Fathoms.	Metres.			12 Metres.	9 Metres.	6 Metres.	3 Metres.	
18–20	33–36½	4·6	Up to 15 min.	—	2	3	7	15
			15–25 „	—	5	5	10	23
			25–35[1] „	—	5	10	15	33
			35–60 „	5	10	15	25	57
			60–120 „	10	20	30	35	97
			Over 120 „	30	35	35	40	142

For ordinary diving work the table limits the stay on the bottom in such a way that the diver can come up safely within half an hour. This is desirable for many reasons: after prolonged stays on the bottom at great depths the time required for safe decompression, even by the stage method, is far too long; and with uniform decompression many hours would certainly be needed at the greatest depths.

[1] Ordinary limit of time.

The method of stage decompression was very thoroughly tested on goats, and compared with the old method of uniform decompression. The result was to show, we think, beyond all question that the stage decompression method is greatly superior, particularly for diving work. Even when the rate of decompression was much too fast by either method, stage decompression proved considerably safer. The accompanying table (Table VI.) shows a number of results obtained with the same animals and under the same conditions, except that the method of decompression was varied. It should be remarked that in each series, excepting C, the rate of stage decompression was less slow than what was calculated to be required for goats in order to prevent all symptoms, and considerably so in series B, D, and E. The occurrence of a few slight symptoms was therefore expected. It will be seen, however, that deaths and severe symptoms were entirely eliminated by the stage decompression, whereas a number of cases occurred with uniform decompression in the same time, besides a much greater number of slight cases.

TABLE VI

Absolute Pressure 6 *Atmospheres*

Series.	Exposure in Minutes.	Decompression in Minutes.	Number of Goats.	Stage Decompression.			Uniform Decompression.		
				Cases of "Bends."	Severe Symptoms.	Deaths.	Cases of "Bends.'	Severe Symptoms.	Deaths.
A	15	31	35	5	0	0	13	3	1
B	30	31	6	2	0	0	4	1	0
C	30	68	14	0	0	0	7	0	0
D	120	70	13	4	0	0	7	2	0
E	120	92	19	3	1	0	3	5	1
F	180	133	10	2	0	0	5	0	0
Total			97	16	1[1]	0	39	11[2]	2

With goats we found it necessary to provide for parts of the body taking as much as forty-five minutes to become half-saturated or half-desaturated with a given alteration of pressure. For man we therefore considered it necessary to provide for parts requiring seventy-five minutes, as the respiratory exchange per unit of body weight in man is three-fifths that of goats.

[1] Paralysis of foot lasting 1 hour.

[2] 3 cases of paraplegia, 4 of temporary paralysis, 2 of dyspnœa, and 2 of undefined illness.

A number of experiments in the steel chamber at pressures up to $6\frac{1}{2}$ atmospheres were carried out on men, with stage decompression; and many dives in the sea to pressures of from 4 to

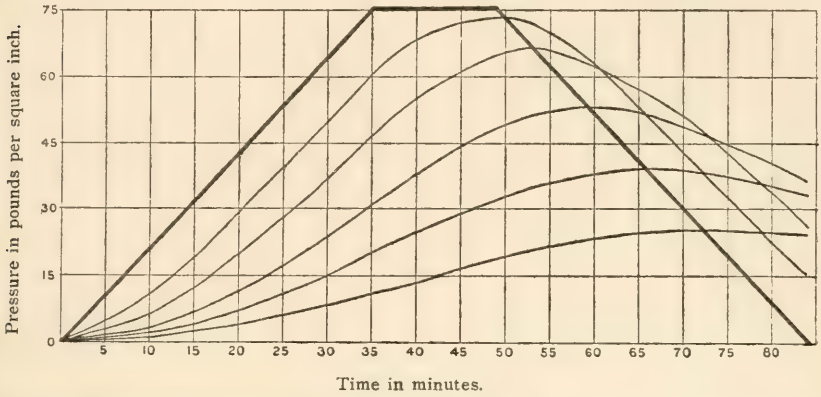


FIG. 2.—Diving to 28 fathoms by old method. The thick line represents the air-pressure. The curves, from above downwards, represent respectively the variations in saturation of parts which half saturate in 5, 10, 20, 40, and 75 minutes.

$7\frac{1}{3}$ atmospheres have also been made by Lieutenant Damant and others, with the time-limits and stage decompression recommended in the new diving tables. No symptom of caisson disease has, however, been observed, so that the new method

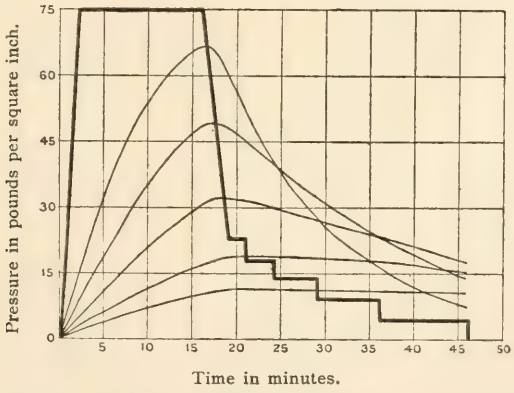


FIG. 3.—Diving to 28 fathoms by new method. The curves, from above downward, represent respectively the variations in saturation of parts of the body which half saturate in 5, 10, 20, 40, and 75 minutes. The thick line represents the air-pressure. Diver 14 minutes on the bottom and 46 minutes under water.

appears to be practically successful. The old method was to go down and come up slowly at a rate of about 5 ft., or $1\frac{1}{2}$ metres per minute. The accompanying diagrams show the

calculated degree of saturation of different parts of the body during a dive to 6 atmospheres pressure for fourteen minutes with the old and the new method. It will be seen at once that the slow descent adds greatly to the danger, while during most of the uniform ascent many parts of the body are actually increasing in saturation; so that by the old method a diver runs a very serious risk of death or paralysis when he reaches surface. By the new method this risk is avoided, and the total time under water is reduced to nearly half. To obtain equally safe results by the method of uniform decompression it would, to judge from the experiments on goats, be necessary to extend the duration of decompression to several hours, the reason being that, in the case of short exposures to high pressure, not only is time wasted during the first half, or two-thirds, of the uniform decompression, but the saturation of most parts of the body continues to increase very seriously, so that at the end the decompression rate is far too fast unless the process is made very slow indeed.

After long exposures to compressed air, as in work in caissons and tunnels at moderate pressures, the saving in time by stage decompression is not so striking; but very substantial gains in convenience become possible. Time, however, forbids me from entering further into this subject, and I must now return to work in mines.

One of the most formidable difficulties met with in the deep mining which is now becoming so common is the great heat which is encountered. It is well known that the deeper we penetrate the earth's crust the higher is the natural temperature of the rock. The rate of increase is usually about 2·5° C. per 100 metres. At some places it is more than this: at others less. At Johannesburg, for instance, the increase is only 0·9° per 100 metres, while in Cornwall it is 3°. At a depth of 1,000 metres, which is now becoming common, the natural rock temperature is usually about equal to the body temperature. The air temperature in a mine may be either above or below the natural rock temperature. Fresh air direct from surface, or the evaporation of moisture, may cause a local reduction in mine temperature. On the other hand the slow oxidation of mineral substances, such as iron pyrites (FeS_2), very commonly causes the mine temperature to rise considerably above the original rock temperature. Miners are thus

much exposed to excessive heat, and the influence of this on their working powers and health is a matter of great practical importance.

In some of the mines of Cornwall the heat is probably as trying as in any place where men have to live and work; and my observations there led me to make experiments on a man's power of remaining in and working in warm air. It is of course well known that men can remain for a short time in extremely hot air, if it is dry. A temperature of 100° C. in a Turkish bath, or even a much higher temperature, can easily be borne for a few minutes; but there is surprisingly little information as to what temperature a man can continue to withstand for hours at a time during his ordinary occupation. My observations were made on several persons, partly in mines and partly in artificially heated rooms.[1]

One main result was that in still air, during rest, and with the subject of the experiment stripped to the waist, the maximum temperature which could be borne for several hours without marked pathological symptoms was 31° to 32° C. (88° to 90° F.) by the *wet-bulb* thermometer. Neither the actual temperature by the dry-bulb thermometer, nor the degree of humidity, nor the percentage of moisture in the air, mattered by itself. The determining factor was simply the wet-bulb temperature. If this exceeded 31° to 32° (the actual critical point seemed to vary slightly in different individuals), the body temperature began to rise steadily. The accompanying diagram shows the results of several experiments made on myself.

It was somewhat remarkable that when the air temperature was just above the critical point, the rise of body temperature did not slacken or cease as the difference between body temperature and wet-bulb air temperature began to increase. Actually the rate of rise of body temperature seemed to increase rather than diminish. The reason for this is the fact, clearly proved in some quite recent experiments by Dr. Sutton, of Oxford University, that the respiratory exchange, and consequently the heat production in the body, rises very markedly with even a slight increase in the rectal temperature. Hence the heat-loss cannot catch up the heat-production, and the body is in a "vicious circle."

[1] Details of part of these experiments will be found in the *Journal of Hygiene*, vol. v. p. 494.

A rise of 2° C. over the normal day body temperature was sufficient to produce much discomfort—a rapid pulse rate, and marked dyspnœa on exertion. A greater rise than this produced alarming symptoms when any considerable exertion was made, as in climbing ladders underground.

In a good air current the critical wet-bulb temperature was found to be about 2° C. higher. During work, on the other hand, the critical wet-bulb temperature was considerably lower—about 26° to 27° with fairly hard work in still air.

That the wet-bulb temperatures should be the determining

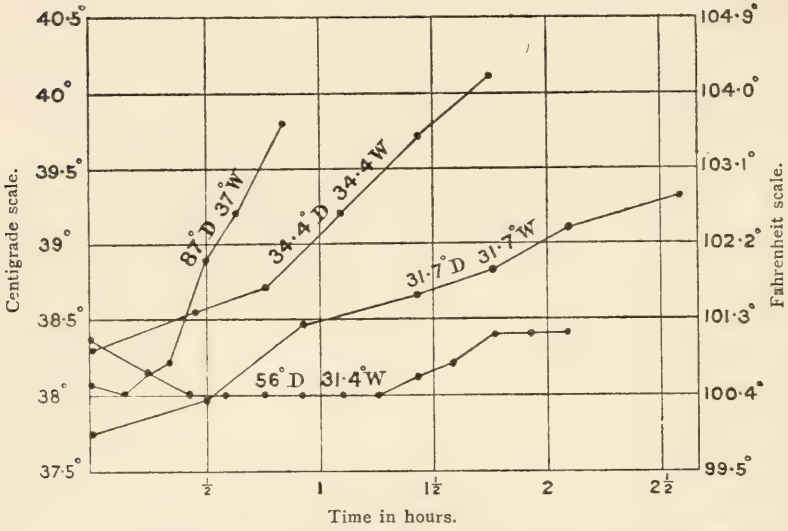


FIG. 4.—Variations of rectal temperature during rest, stripped to the waist, at various air-temperatures.

D = dry-bulb air-temperature. W = wet-bulb air-temperature.

factor is exactly what might have been predicted on physical grounds; and as the body, unlike the wet-bulb of a thermometer, is itself a source of heat, it is equally intelligible that moving air raises the critical wet-bulb temperature, and increased heat-production in the body lowers it.

A further point brought out strikingly in some of the experiments was that the sweating produced by heat depends primarily on the skin temperature, and not on the internal temperature of the body. There is quite commonly a fall in the rectal temperature at the time when most profuse sweating breaks out on going into warm air. On the other hand, sweating does not

occur in hot air until the skin temperature reaches a certain point. If the skin is cold to begin with it may be half an hour or more before sweating breaks out in a very warm room, whereas there will be profuse sweating within a minute if the skin is warm to start with.

I found that the Cornish miners were frequently employed in places where the wet-bulb temperature was from 30° to 38°. It might be supposed that, under such circumstances, cases of heat-apoplexy would be common; but I never could hear of any such cases, nor did I find, even in the hottest places, that the men allowed their temperatures to rise more than very slightly. What they did was simply to come out and rest in a cool place as soon as they felt that they were getting too hot. In fact, they seemed to be nearly always resting in this way. At a wet-bulb temperature of about 27° the amount of work done by a miner begins to fall off, and as the wet-bulb temperature rises further the work done gradually diminishes to a vanishing point. It may be that a miner's health sometimes suffers from the heat; but I could not find any clear evidence of this, and the men working in hot mines seem to be usually quite healthy. What undoubtedly suffers very heavily is the pocket of the mine-owner.

On the other hand, mine-horses often die of heat-apoplexy; and so fatal is the heat to horses that their employment is avoided in some of the hotter mines. They are liable to be worked too hard in a warm mine, just as soldiers are liable to be overmarched in hot weather; whereas the miners, who are perfectly free to follow the promptings of nature—for instance, to take off their clothes, stop working, or go into a cool place, or even into cool water, when they are too hot—escape without harm.

It seems clear that, for the economical working of a mine, the wet-bulb temperature should not in general be allowed to rise beyond about 27°—unless, perhaps, where there is a good air-current. To maintain this limit in the ordinary working places does not seem to be very difficult, provided the right measures are taken in laying out the ventilation. This matter will soon have to be studied much more closely by mining engineers than has been the case hitherto.

I should like, in conclusion, to point a moral, if I may, in connection with the hygienic regulation of engineering and

manufacturing work. No one doubts that the health, efficiency, and comfort of our working population are matters of the utmost importance. But the desirability of properly investigating the hygienic conditions of various industries is scarcely yet recognised as it ought to be. There is plenty of talk and a large number of regulations; but real knowledge—the indispensable basis of effective action—is too often lacking, and can be gained in no other way than by careful and detailed observation and experiment. This can be illustrated from all branches of hygiene—for instance, by the immensely important knowledge patiently gained during the last few years as to the nature and means of spread of various infective diseases.

I wish, however, to emphasise the same fact in connection with industrial hygiene; and perhaps the specific problems just discussed may enable me to do so. They concern the physical and chemical characters of the air in its relation to certain industrial employments. Insufficient study has, in spite of the best intentions, led to many mistakes in connection with these employments. First, as regards work in compressed air, we find on the one hand that divers have been more or less hampered or endangered by that somewhat rare condition, poisoning by carbon dioxide. But if we turn to men employed in compressed air in tunnels, etc., we also find the conditions—in England at least—reversed in a curious way. It has become a common popular belief that, provided the carbon dioxide percentage is low enough, all must be well with any kind of air. For instance, in the case of the large tunnel at present being constructed in compressed air under the Thames at Rotherhithe, London, the County Council, regardless of the enormous expense, has prescribed that, in view of the danger of caisson disease, the proportion of CO_2 shall not exceed that in the average air outside by more than 4 volumes per 10,000. It is, of course, not conceivable that by increasing the air supply to such an extent caisson disease can be prevented. The chief effect of the large air supply seems to be that the tunnel is very warm, as in consequence of the large quantity of air it is not effectively cooled between the compressors and the tunnel. The large air supply is thus probably doing more harm than good; and the absence of effective regulations for preventing caisson disease lays the County Council open to criticism in view of the long-existing knowledge of the subject.

Again, the well-intentioned regulation hitherto in force in the British, German, and other navies, that a diver should always descend very slowly, has probably cost many a diver his life.

To turn to the mining industry, one finds that often no expense is spared, and burdensome regulations may be imposed by law, in the endeavour to cure by unsuitable means evils for which a little real investigation would have shown an effective cure. In the Cornish mines, for instance, more ventilation was being provided as a remedy for the evils caused actually by stone dust and ankylostomiasis. The increased ventilation was apparently only aggravating the evil by making the working places drier and more dusty, just as in coal mines increased ventilation has, by itself, often increased the danger of colliery explosions by making the coal dust drier. Courrières Colliery, where 1,100 men were killed by a coal-dust explosion last year, was probably one of the best-ventilated mines in Europe.

As regards heat and moisture in the air, we have in England the curious anomaly in our Factory Act that the wet-bulb temperature in cotton factories, where women are employed all day, is expressly permitted by law to rise to even 37°, provided that the proportion of CO_2 does not exceed 9 volumes per 10,000! I do not for a moment mean to imply that any manufacturer would permit such a state of matters to exist in his factory, or that the workers would stay for an hour in such an impossible atmosphere; but the extemely well-meant English regulations as to temperature and humidity in the air of factories furnish one instance out of many, illustrating the need for more knowledge and investigation.

Such knowledge must be gained to a large extent on the spot, and not merely in a laboratory. Men who are tied to their work in a laboratory are often called upon to express opinions about matters of industrial hygiene without having any adequate opportunity of personally investigating the actual conditions. It is almost invariably the case, however, that investigations on the spot are essential, and that discussion with engineers, managers, and workmen throws entirely new light on the subject-matter. For one thing, the engineers and managers help us, beyond everything, to think of things quantitively and in their relations to other things. This lesson

is one which is often greatly needed in our branch of science. In spite of the inspiring examples of such men as Pettenrofer or Paul Bert or Parkes, we seem constantly in danger of forgetting it. We should progress hand in hand with the development of each industry, and be ever ready to help the engineer or manufacturer. It is only by doing this on the one hand, and by keeping in close and living touch with physiology and pathology on the other, that industrial hygiene can properly fulfil the very important duties which human progress has assigned to it.

THE GREAT SCANDINAVIAN OVERTHRUST

By J. W. GREGORY, F.R.S.

Professor of Geology, University of Glasgow

Scandinavia and Scotland are geologically nearly akin, and some of the difficult problems of Scottish geology may be solved by the Scandinavian evidence, which is often bolder and simpler.

The two lands were originally both part of the old Continent of Arctis; and they both have a similar foundation of crystalline schists and gneisses, which in Scandinavia are accepted as Archean. In both countries the older rocks are covered by wide sheets of pre-Cambrian sandstones—the Torridonian of Scotland and the Algonkian series of Scandinavia. Both countries have fossiliferous Cambrian rocks along their north-western edge, with a wider development of Lower Palæozoic, and even younger sediments to the south-east of the crystalline mass. That the schists of Scotland were once connected with those of Scandinavia is suggested by their frequent coincidence in strike, indicating that the structural grain of the countries was continuous across the North Sea. The geological connection has, however, often been geographically broken, and the direct land bridge apparently existed last in Pliocene times.

The student of crystalline schists in Scandinavia has the advantage over the Scotch geologist of the presence, in many localities, of fossiliferous Lower Palæozoic rocks in close association with the schists. In the Scottish Highlands, on the other hand, the fossiliferous rocks are restricted to a band along the north-western edge, except for a couple of localities containing doubtful worm tubes. The structure of Scotland, in its turn, helps to elucidate that of Scandinavia; for it was research on Scottish geology that explained the occurrence of fossiliferous sedimentary rocks beneath series of crystalline schists and gneisses. Murchison attributed this

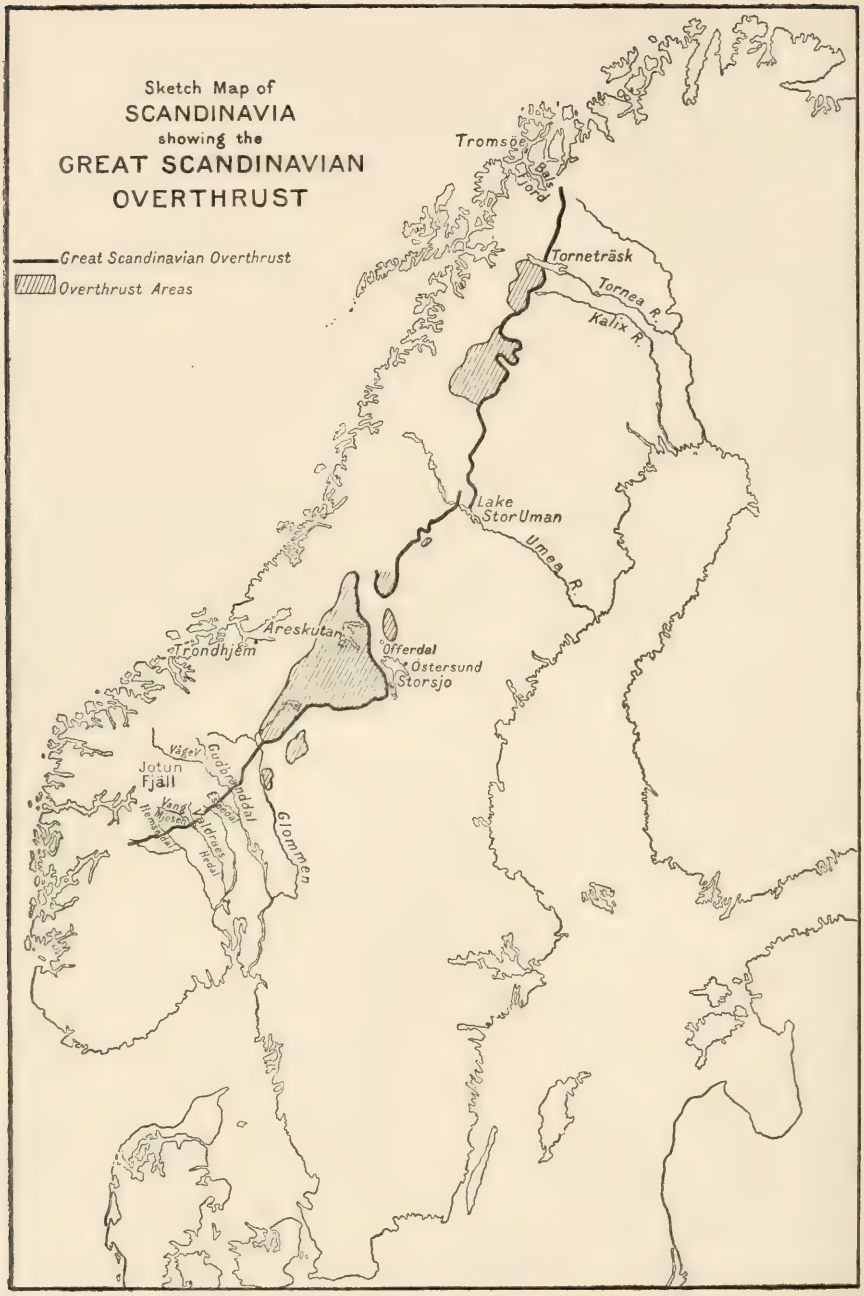
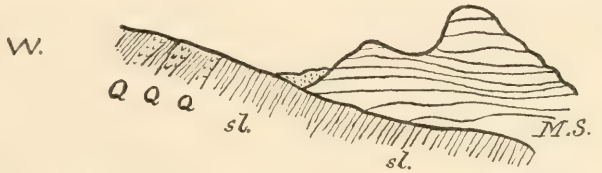


FIG. 1.

[The Valdraes is the valley marked above the name.]

arrangement, in the case of the Scottish Highlands, to selective metamorphism having converted the upper beds into schists, while leaving the lower beds unaltered. This view was also adopted in Scandinavia. It assumed, in accordance with the law of superposition, that the overlying beds must be the younger, and the chemical difficulties of selective metamorphism were left for subsequent explanation. That these difficulties were great was evident in Scandinavia from the observations made by Gumaelius in Offerdal during 1869. He then showed, in a section reproduced as fig. 2, the existence of a block of mica schist overlying phyllites or clay slates, with relations which selective metamorphism could hardly explain.[1]

Murchison's theory was overthrown in Scotland by the discovery that the crystalline schists had been thrust into positions where they appear to rest conformably on younger



Q = Quartzite. *sl* = slate. M.S. = Mica Schist.

FIG. 2.—Section in Offerdal by Gumaelius.

beds. And the same explanation has been demonstrated in Scandinavia, although there it appeared at first almost incredible owing to the vast scale of the phenomena.

The literature of the Scandinavian overthrust is somewhat scattered, and it is mostly written in Swedish or Norwegian. Hence a brief statement of some conclusions and reference to the original authorities may be of value to British geologists. It has recently been my privilege to examine one of the typical overthrust sections on the shores of Lake Torneträsk in Swedish Lapland. For directions and kind help in this visit, and for showing me the material bearing on this question in the museums at Stockholm and Upsala, I owe my warmest thanks to Prof. Högbom of Upsala, Dr. Gunnar Anderson, Director of the Geological Survey of Sweden, and Dr. Holmquist, of the Technical High School of Stockholm. Nor must I omit mention

[1] This section was referred to by Törnebohm in 1873, *Sver. Geol. Unders. Ajhandl.* No. 9, p. 42; but it apparently remained in manuscript until it was published by Högbom in 1894.

of my indebtedness to the writings of Herr A. E. Törnebohm, late Director of the Geological Survey of Sweden, to whose work the present interpretation of the complex mountain structure of the High Fells of Scandinavia is so largely due.

Scandinavia consists geologically of a foundation of Archean and pre-Cambrian rocks, which are exposed over nearly all Eastern and Southern Sweden; they also form the fringe of islands along the Atlantic coast and most of the rugged southern provinces of Norway between Christiania and Bergen. The second important constituent is a band of schists and gneisses, which forms the mountain axis of Scandinavia, parallel to the Atlantic coast. It was doubtless once part of an old fold-mountain chain, which has now been cut down into a dissected pene-plane, wherein the existing ridges are independent of the heights formed by the original folds. The schists of this region are associated with thick masses of sandstone and conglomerate —the sparagmites and Dala Sandstone. Some of these rocks were once believed, as by Murchison, to be Old Red Sandstone; but they are now generally recognised as of pre-Cambrian age, and accepted as members of the Algonkian system. The schist belt also includes some fossiliferous rocks; and it has been held that the schists themselves are only Palæozoic sediments that have undergone thorough alteration. They were divided by Törnebohm in 1872 into two series, a lower or Seve Group, and an upper or Köli Group, and both were then regarded as Silurian or even post-Silurian.[1]

In addition to these rocks, which are doubtfully assigned to the Palæozoic, there are some slightly altered, sedimentary rocks, many of which are fossiliferous, so that their age is known. These rocks include representatives of the four oldest Palæozoic systems. Here and there from Lapland to south-western Scandinavia are areas of coarse sandstones, which are regarded as probably Devonian. The Lower Palæozoic rocks include members of the Silurian, Ordovician, and Cambrian; and their classification is somewhat complex, as they are developed with two very different facies—the eastern and the western.

The eastern facies includes normal sedimentary rocks, of which the upper members are shown by their fossils to include

[1] A. E. Törnebohm, "En geognostisk profil öfver den skandinaviska fjällryggen mellan Österund och Levanger," *Öfver K. Svens. Vet. Akad.* 1872; also *Sver. Geol. Unders. Ajhandl.* Ser. C, No. 6.

representatives of the Silurian and Ordovician systems; while beneath the fossiliferous rocks there are beds of alum shale and sandstone which, from their stratigraphical position, are referred to the Cambrian. These eastern rocks are but little altered, and they occur in simple regular sequence, with abundant limestones and fossils.

The Lower Palæozoic rocks of the western facies are lithologically strikingly unlike those assigned to the same age in districts farther to the east. The great bulk of the western rocks are schists; there are but few limestones, and fossils are found only in isolated deposits, which range in age from the Lower Cambrian to the Silurian. The striking lithological differences between the eastern and western rocks is explained as being partly due to more intense metamorphism in the western area; but this explanation is not alone adequate, as the rocks when first deposited must have been essentially different in composition in the two areas. It is therefore further explained that the "Silurian" rocks of the western area are due in part to extensive eruptions of basic rocks, while sediments were quietly accumulating in the seas to the east.

The Lower Palæozoic rocks of the western facies are themselves subdivided into the eastern and western sub-facies; their relations are somewhat uncertain, and the settlement of this question will be watched with much interest by Scotch geologists, from its analogy to some doubtful points in the correlation of the schists of the Southern Highlands of Scotland. Both the eastern and western sub-facies consist of series of phyllites, clay slates, schists, and gneisses, of which the most highly crystalline rocks belong to the lower division of the eastern sub-facies.

The rocks vary in metamorphism along their strike; though why the most highly metamorphosed areas are distributed as shown in Törnebohm's map is not obvious. Thus the Sul Schists extend from north-north-east to south-south-west in a narrow band 2 miles wide and 80 miles long; and it is marked as strongly metamorphosed for a length of about 22 miles; whereas the adjacent parallel band of the Meraker and Selbu Schists is strongly metamorphosed for 45 miles farther to the south-south-west. In both sub-facies there are some fossiliferous beds: namely, the Höilandets group of Trinucleus Sandstone age (Ordovician) in the western series, about 25 miles south-south-west from Trondhjem; and the Sul slates, containing

graptolites belonging to the lower part of the true Silurian, in the eastern series. These fossiliferous beds are held to support the view that the schists of the area are altered Lower Palæozoic rocks. This, however, is the one conclusion in Scandinavian geology which foreign geologists may be most excused if they hesitate to accept, until further evidence has been published that the fossiliferous beds cannot be younger rocks folded or faulted in among older schists. The solution which Prof. Bonney gave of the same problem in the Lepontine Alps may be applicable to the schists of the Trondhjem district.

The belief that these schists were all Silurian was, however, naturally adopted at first, because unaltered fossiliferous Lower Palæozic rocks are found in places beneath wide sheets of schist and gneiss. It therefore appeared necessary to accept the upper beds as the younger in age. But it has been proved that, as in Scotland and the Alps, the superposition of the schists is due to earth movements. And in Scandinavia the overthrusting has taken place on a scale greater than has been established in any other part of the world.

The development of these views may be seen from the successive explanations of the geology of Åreskutan in Jemtland, one of the best known Swedish mountains (4,645 ft.). The lower eastern and western slopes of this mountain consist of the normal Lower Palæozoic rocks of the eastern facies; they include the Cambrian alum shales, above which are more shales, and the Pentamerus Limestone of the base of the true Silurian. The whole of the upper part of the mountain consists of crystalline schists of the Seve Group; they include hornblende schist, mica schist, crystalline limestone, and garnetiferous gneiss. The base of the crystalline schists is a quartzite or quartz-schist, which is in places a conglomerate. "The contact between this quartzite and the Silurian clay rocks I saw laid bare," says Törnebohm,[1] "in a small stream that descends from the western side of Åreskutan. The dip is here not more than 15° or 20° to the east, and the superposition is very clear. The boundary between both formations stands out very definitely, yet without any marked discordance. Over the quartzite, which is not very thick, follow first hornblende schists, which alternate with mica and quartzitic schists, and include some small layers, only a few inches thick, of white crystalline limestone; further up come

[1] Törnebohm, *Afhandl. Sver. Geol. Unders.* No. 9, 1873, p. 41.

a somewhat thick quartzite schist, wherein occur the copper ores of Åreskutan; and then follow gneiss-like rocks (which sometimes include hornblende and sometimes garnets as accessory constituents), and they, with alternations of hornblende and mica schists, extend up to the summit of the mountain."

The same sequence is exposed on the eastern side of the mountain, and Törnebohm therefore naturally concluded that "the schists of the Seve Group, in spite of their crystalline structure and their primæval aspect, are younger than the surrounding Silurian deposits, and that between them occurs a definite geological boundary which is sometimes marked by beds of conglomerate."[1]

This conclusion is represented in a section across Åreskutan which is reproduced as fig. 3. Ten years later Törnebohm recognised that the superposition could not be trusted, as the relations

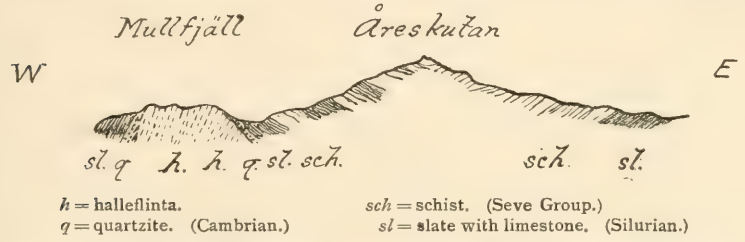


FIG. 3.—Section through Åreskutan after Torneböhm, 1872, representing the Are schists as post-Silurian.

of the Dala Sandstone (now recognised as Algonkian) had been in places inverted by overthrusting; but he still accepted the view that the Seve Group, with the Vemdal quartzite which he regarded as its base, is later than the underlying Lower Palæozoic rocks, and supported this conclusion by fresh evidence from the district of Herjedalen.[2]

The demonstration by Prof. Lapworth and by Dr. Horn, Dr. Peach and their colleagues of the Scottish Geological Survey, that the superposition of schists over normal sediments in the north-west Highlands of Scotland was due to overthrusting, encouraged Törnebohm to believe that the same process was the cause of the perplexities of mountain structure in

[1] Törnebohm, *Afhandl. Sver. Geol. Unders.* No. 9, 1873, p. 42.

[2] A. E. Törnebohm, "Om Vemdalsqvartsiten och öfriga qvartzitiska bildningar i Sveriges sydliga fjälltrakter," *Geol. För. Förh.* vol. vi. (1883), pp. 274–94. pl. xii. and xiii.

Scandinavia. In 1888 he redescribed the geology of Åreskutan,[1] and identified the schists and gneisses of the summit of the mountain as pre-Silurian rocks, pushed from the west over the lower but younger Palæozoic sediments. This view is represented in fig. 4 from Törnebohm's memoir of 1896.

In 1891 Törnebohm explained other cases of the apparent interstratification of slates and quartzites with gneisses as due to inversion by folding. Thus on the northern foot of the Jötun-Fjäll in Norway, on the southern shores of Lake Våge, the apparent sequence consists of the following beds, all of which are dipping southwards: (5) upper gneiss, (4) upper quartzite, (3) clay slate, (2) lower quartzite, (1) lower gneiss. Törnebohm explained this arrangement as due to an isoclinal, by which the quartzite and gneiss are repeated on

FIG. 4.—Section through Åreskutan after Torneböhm, 1896, showing the Åre schists as pre-Silurian.

both sides of the slates.[2] According to this interpretation there are only three beds, and the gneiss is the oldest.

This conclusion was, however, rejected by Björlykke, who in 1894 accepted the fact that much of the so-called Mountain Quartzite (*Höifjeldskvartsen*) of the Norwegian Fells was a gneiss and not a quartzite; and he claimed that this gneiss was of post-Ordovician age, and that the crystalline rock had been originally deposited unconformably on the unaltered, older Ordovician beds.[3]

In 1905 Björlykke issued as No. 39 of the *Norges Geologiska Undersögelse* a work on the mountain structure of Central Norway, in which he maintains that the upper sparagmite group is of Devonian age, and that, for that area, "the theory of overthrusting must be abandoned." For the geology of

[1] A. E. Törnebohm, "Om fjällproblemet," *Geol. För. Förh.* vol. x. (1888), pp. 328–36.

[2] A. E. Törnebohm, "Om högfjällsqvartsiten," *Geol. För. Förh.* vol. xiii. (1891), p. 41.

[3] K. O. Björlykke, "Höifjeldskvartsens nordostligste udbredelse," *Norges Geol. Undersög.* No. 14; Aarbog for 1892 og 1893 (1894) pp. 64, 73, 74.

Mount Åreskutan he apparently accepts the suggestion of Reusch, that its upper gneisses are altered eruptive rocks. From the same memoir it appears that Schiötz, in 1902, accepted the action of overthrusts to explain the structure of Österdal in Eastern Norway.

In 1894 Herr Törnebohm's views received the powerful support of Prof. Högbom, now of the University of Upsala, who demonstrated the truth of the overthrust theory by careful mapping of the High Fells of Jemtland. His results were published in a monograph,[1] and illustrated by a geological map of the province on the scale of 1 to 500,000. His survey proved that the overthrusting has taken place on a scale even greater than in Scotland. Two years later followed Dr. Törnebohm's important memoir,[2] which described the geological structure of the main High Fells both of Norway and Sweden, and extended the overthrust explanation to the districts to the south-west of Jemtland.

The surveys of Törnebohm and Högbom leave no doubt as to the occurrence of a great overthrust of pre-Cambrian schists over Lower Palæozoic sediments. The main overthrust mass covers an area of some 5,200 square miles; this vast sheet of rock was thrust from west to east over the underlying fossiliferous sediments. The evidence is clearest in the case of some outliers of the schists, which have been cut off by denudation from the main overthrust mass. The best known of these outliers are at Offerdal, a locality to the north-west of Östersund and thirty miles east of Åreskutan. Offerdal is a valley running from north-west to south-east and containing the upper arm of Lake Nälden. The floor of the valley is occupied by the true Silurian beds, which are thrown into many small folds, and are often isoclinals dipping to the west (fig. 5). The valley is bounded to the north by a plateau, which is cut through by the valley of Lake Landösjön; the plateau and the area to the north of that lake are formed by overthrust mica schists and crushed Algonkian conglomerates and

[1] A. G. Högbom, "Geologisk Beskrifning öfver Jemtlands Län," *Sver. Geol. Unders. Afhandl.* Ser. C, No. 140 (1894), 107, p. 1, pl. and map.

[2] A. E. Törnebohm, "Grunddragen af det Centrala Skandinaviens Bergbyggnad," *Handl. K. Svens. Vet. Akad.* vol. xxviii. No. 5 (1896), 210 pp. 4 pl. and geological map of Central Scandinavia, on scale of 1 to 800,000 (with German Summary pp. 179–97).

quartzites. The southern side of the Offerdal valley is formed by a block mountain known as Alsen, which is built of the same rocks.

According to Prof. Högbom's map, the Pentamerus Limestone (*i.e.* Silurian of the Llandovery Series) can be traced all round the foot of the Alsen outlier; and looking across Offerdal to the north, the superposition of the schists above the limestones is shown in a section, reproduced as fig. 5.

The maps and sections of both Törnebohm and Högbom appear convincing that the only satisfactory explanation of the facts is that the schists have been overthrust above the Lower Palæozoic sediments.

From Jemtland, the overthrust has been traced south-west into Norway and northward into Lapland. The evidence in the far north has been collected by several observers, including

s Contorted Silurian (chiefly Upper Silurian). *c* = Crushed Sparagmite.
sch = Schists. (Seve Group.) T.P. = Thrust Plane.

FIG. 5.—The north bank of Offerdal, after Högbom.

Törnebohm, Högbom, Holmquist, Sjögren,' and Svenonius.[1] Prof. Sjögren[2] has described the sections around Sulitelma, and Dr. Holmquist[3] the wide area of schists thrust over sediments assigned to the Silurian, to the south-east of Sulitelma and south-west of Qvikkjokk. To Dr. Holmquist[4] is also due the most detailed account of the overthrust area to the south of Torneträsk, the most northern of the great Swedish lakes. The evidence at Torneträsk is very clear, and, by the kindness of Herr H. Lundbohm of Kiruna and the Traffic Manager of

[1] A bibliography has been recently given by Högbom, Nörrland, 1907, pp. 108–9.

[2] H. Sjögren, "Om Sulitelma-områdets bergarter och tektonik," *Geol. För. Förh.* vol. xviii. (1896), p. 346.

[3] P. J. Holmquist, "En geologisk profil öfver Fjellområdena emellan Kvikkjokk och Norska Kusten," *Sver. Geol. Unders. Afhandl.* Ser. C, No. 185 (1900), 100 pp. 2 pl.

[4] P. J. Holmquist, "En geologisk profil öfver den skandinaviska fjällkedjan vid Torneträsk," *Geol. För. Förh.* vol. xxv. (1903), pp. 27–78, pl. i.–iii. And "Bihang till Törneträskprofilen," *ibid.* pp. 373–90, pl. xii.

the Lapland Railway, I was enabled to spend a few hours at Kaisepakte, where the thrust plane is most accessible.[1]

A bluff of rock here rises steeply above the southern shore of the lake; the lower part of the slope consists of a massive pink granite. Then follows a series of brown nodular shales, with some layers of conglomerate; next a green shale and a brown nodular shale with some concretions; then follows a bed of dark blue massive quartzite. The shales are normal sedimentary rocks resembling in aspect some of our Tarannon shales. A fossil has been found in them at Luopahta, a few miles farther to the east. Holmquist[2] quotes an opinion based on it that the beds are of the age of the Chasmops Limestone (Middle Ordovician); but the fossil appears to be indeterminable, though its presence encourages the hope that better material will reward further search. Above these Lower Palæozoic sediments comes a sheet of cataclastic schists, some of which still retain the characters of augen-gneiss; but the main mass of rock has been broken down into a mylonite. This shattered rock has been named "Kakarit" by Svenonius. All stages of mylonitisation may be seen, including crushed gneiss, banded felspathic quartzite, and banded granulites; the extreme stage in the dynamo-metamorphism is reached in some fine-grained pseudo-phyllites, which look like simple slates.

The overthrust rocks are intensely crushed and contorted, great blocks being composed of layers twisted into complex folds and overfolds. The underlying sediments, on the other hand, often remain horizontal or with a dip of only 2°. Examination of this section is convincing that the crystalline rocks that form the bluff of Kaisepakte have been thrust over the unaltered, undisturbed underlying sediments. The descriptions by Dr. Holmquist of the adjacent districts to the south of Torneträsk; by Törnebohm[3] of the country to the north of the lake at the head of Balsfjord, to the south-east of Tromsöe; by Sjögren of Sulitelma; and by Holmquist of the country south of Sulitelma, show that this overthrust traverses the whole length of Norrbotten, the northernmost province of Sweden.

[1] During my visit I had the benefit of the company of Herr Ljüstrom and Herr Sundius of Upsala.

[2] Holmquist, *Geol. För. Förh.* vol. xxv. p. 38.

[3] A. E. Torneböhm, "Om formationsgrupperna inom det nordligaste Skandinavien," *Geol. För. Förh.* vol. xxiii. pp. 206–17.

There is also evidence of the overthrusting across Westerbotten, between Norrbotten and Jemtland. The overthrust can indeed be traced from 69° N. lat. in Norwegian Lapland across seven degrees of latitude in Sweden, till the line recrosses the frontier and continues for 150 miles farther into Norway. Its course in Southern Norway was traced by Törnebohm across the valleys of the Glommen, of Gudbrandsdal, Espedal, the Valdres valley (Hedal), and Hemsedal. His conclusions were supported by Reusch's[1] description of the country around Vangs Mjösen and Slidre, in the upper part of the Valdres Valley, where the Archean granites are overthrust over phyllites and quartzites assigned to the Cambro-Silurian. And the course of the great overthrust has been continued westward round the Sognefjällen to the Hardangerfiord, by the work of Reusch, Rekstad, and Björlykke,[2] and by Rekstad in the Hemsedalfjällen.[3]

The Scandinavian overthrust is therefore on a colossal scale. It follows the main mountain chain of Scandinavia throughout its entire length. Its length, according to Törnebohm, is about 1,800 kilometres (over 1,100 miles). It is therefore on a much larger scale than in Scotland, where the length of the overthrust from Glenelg to its northern end at Whitten Head is about 100 miles. The width of the overthrust is even more startling. Törnebohm claims that the overthrust masses, which are still 1,500 metres thick, have travelled eastward for a distance of eighty miles. He remarks that "such an immense width is something never yet precedented in the annals of geology, and he does not conceal from himself the fact that its possibility will be generally doubted. But after many years of investigations he has come to the conviction that only by such a great overthrusting can the actual relations be explained; so he is not afraid to express this conviction boldly." Törnebohm claims that the width of the overthrust is not disproportionate to its length. The demand made on the strength of the rocks is, however, at first staggering; so it is not surprising that the development of the overthrust hypothesis in Scandinavia met with some opposition.

[1] Hans Reusch, "Höifjeldet mellem Vangsmjösen og Tisleia (Valdres)," *Norges Geol. Undersög.* No. 32; Aarbog for 1900, pp. 45–88.

[2] "Fra Hardangervidden," *Norges Geol. Undersög.* Aarbog for 1902, No. 2.

[3] *Ibid.* 1903. The south-western extension of the overthrust has been described by Törnebohm, "Om den skandinaviska fjällkedjans sydvestände," *Geol. För. Förh.* vol. xxv. (1903), pp. 282–8.

The criticisms have followed three main lines. (1) The post-Silurian age of the schists and gneisses overlying the sediments is still maintained by several Scandinavian geologists. (2) The superposition of the older beds has been attributed by Svenonius to complex overfolding; he explained the succession of the rocks in Norrbotten by contortions similar to those formerly introduced in Swiss geology (fig. 6, after Svenonius). (3) The invocation of numerous overthrusts instead of one vast movement.

The third hypothesis has been advanced by Dr. Holmquist, from the evidence collected in his careful study of the districts to the south of Torneträsk. He holds that instead of there having been one vast overthrust, which in that area would have to be thirty-five miles or more in width, there have been many shorter overthrusts. The "Silurian" rocks have been thus sandwiched between the crystalline rocks; and,

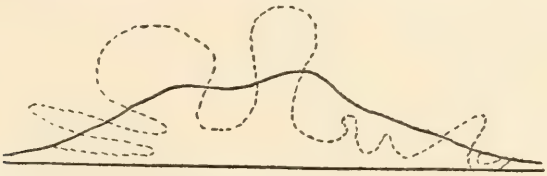


FIG. 6.—Section through Daunevarra, Lapland (after Svenonius, 1896).

according to Dr. Holmquist, the tops of the folds sometimes expand laterally beyond their impressed limbs, like an exaggerated Alpine fan. But these sections have been ridiculed as "mushroom constructions" by Törnebohm, who holds to his faith in one great movement.[2] Dr. Holmquist's view, however, appears to be possible, and it has the recommendation of making less trying demands on the strength of the rocks. The overthrust rock-masses are comparatively thin in proportion to their extent, and it would appear very doubtful whether they could have been thrust forward in a slab by pressure applied thirty miles behind in the case of Lapland and eighty miles distant in Jemtland. We are forbidden to appeal

[1] F. Svenonius, "Om Berggrunden i Norrbottens Län," *Sver. Geol. Undersok. Ajhandl.* Ser. C, No. 126, 1892, pp. 37–41, and "Några Bidrag till belysning af eruptivens betydelse för fjällbildningarna," *Sver. Geol. Unders. Afhandl.* Ser. C, No. 161 (1896), pl. 1.

[2] A. E. Törnebohm, "Om Torneträsk-profilenstydning," *Geol. För. Förh.* vol. xxv. (1903), pp. 83–92.

to a very thick overlying rock cover, or the underlying shales must have been more disturbed. The process must have happened in the fracture zone of the crust and not in the deeper zone of fluxion. Hence if Dr. Holmquist's view be found correct, and could be extended by further mapping to Jemtland, it would simplify the explanation of the crustal movements, and would still leave the Scandinavian overthrust the greatest yet discovered.

The Scottish and Scandinavian overthrusts are accompanied by many of the same phenomena. The most significant difference is that the movements took place in opposite directions; in Scotland the rocks above the thrust planes were pushed westward; in Scandinavia they travelled eastward. The disturbances were therefore doubtless due to changes in the land that occupied the area between the Scandinavian High Fells and the North-West Highlands of Scotland. The thrusts, on both sides, were outwards towards the depressions that probably existed in the Baltic region and off the western coast of Scotland.

Supplementary Note on the Literature

In addition to the literature cited in the text reference may be made to the following. Full bibliographies of the earlier literature are given by Törnebohm in his *Grunddragen*, 1896, pp. 202–5, and by Högbom in his Monograph on Jemtland, 1894, pp. 100–3.

A short summary of the literature on the investigations of 1868–71 is given by Törnebohm, "Till historiken öfver de geologiska undersökningarna i Sveriges fjälltrakter," *Geol. Fören. Förhandl.* vol. vii. 1885, pp. 669–73.

A summary is given by Prof. Högbom in the third section of his paper, "Sur la tectonique et l'Orographie de la Scandinavie," *Annales Géogr.* vol. xi. 1902, pp. 122–33, pl. v.

The course of the overthrust line in Sweden is marked on the geological map of Sweden on the scale of 1 to 1,500,000, issued by the Swedish Geological Survey in 1901.

Many of the memoirs quoted from the *Afhandlingar* of the Geological Survey of Sweden were also published in the *Förhandlingar* of the Geological Society of Stockholm.

THE REPAIR OF A NERVE

By W. D. HALLIBURTON, M.D., F.R.S.

It is not probable that many readers of Science Progress have ever experienced the misfortune of having an important nerve cut across. But those engaged in hospital practice, especially in manufacturing districts where machinery is employed, often see accidents of this nature. The result of such an injury is that the parts of the body which the divided nerve served to link with the central nervous system are destitute of the power to move and to feel. The telegraphic service of the body has been interfered with, and the brain is no longer able to transmit its commands to the motor mechanism, nor to receive communications from that part of the sensory surface which is severed from it by the division of nerve fibres. Many of these cases recover after the lapse of time, and this period can always be shortened if by surgical interference the divided segments of the nerve are sutured together.

If, on the other hand, the injury occurs in the central nervous system, the effects are more serious. Suppose, for example, the spinal cord is divided or crushed, then the main line of communication is no longer capable of conducting nerve impulses up and down, and a large area of the body surface is thrown out of connection with the sensorium. And again, unless the division is a complete one, a certain amount of recovery takes place. But the method of repair is different in this case from what it is in our first example—the division of a nerve.

In the recovery that occurs to a small extent when important conducting paths are cut across in the central nervous system, restoration is not due to the healing of the injured tracts, nor to the regeneration of the divided threads, which are called nerve-fibres; but to the happy circumstance that the complex labyrinth of conducting paths has so many cross connections that it is possible for impulses to avail themselves of these,

and so reach their destination by a new channel. There is absolutely no recovery if the division of the spinal cord is complete, for then all possible channels are equally blocked.

In a nerve, recovery will occur if the division is absolute, and in this case restoration of function is due to the regeneration of the nerve fibres. It is the object of this paper to describe the manner in which this regeneration occurs.

Nearly every one has suffered at some time from minor injuries in the way of skin wounds, and has doubtless for a time experienced anæsthesia or loss of sensation on one side or other of the cut. Some months later sensation returns, and the accident is forgotten. Regeneration of the nerves necessary for this usually occurs without any surgical aid, and and all that remains is a scar. Scar tissue, or cicatricial tissue, as it is technically termed, is a dense kind of connective tissue somewhat stronger and firmer than the ordinary skin. This same kind of tissue is formed in the repair of all injured structures in the body. When, for instance, a muscle or a tendon is cut across, the formation of cicatricial tissue to bridge across the gap is quite sufficient to restore the continuity and uses of the injured organ. If a rope is divided, it does not matter what sort of material—silk, hemp, or cotton—is used to tie the ends together; if the repairing material is sufficiently strong the rope is as good as ever. So it is with the haulage mechanism of the body: a tendon or a muscle can pull upon the bones quite as well as before the accident, even although the repairing tissue is not identical with that which was injured.

But the case of a nerve is different. If a telegraph wire is divided the repairing material must be wire, or at least something capable of conducting electricity. The molecular change transmitted along nerve fibres, and which is termed a nervous impulse, is so peculiarly the property of nerve fibres, that no amount of scar tissue is efficacious in restoring function. Nerve fibres must be mended by nerve fibres and by nothing else. Indeed, a large amount of cicatricial tissue is harmful, for its very density is an obstacle to the successful growth of the new fibres which ultimately penetrate it.

We must never push the telegraphic simile too far in dealing with the nervous system, useful as it is in talking of such matters to students. If a telegraph wire is broken, all that is necessary in healing the damage is to connect the ends

with another piece of similar wire; the two segments of wire which are united are not injured throughout their length, and conduct the electrical impulse as well as ever. In the case of a nerve it is different; the stretch of nerve still united to the central nervous system is spoken of as the central end; this consists of long threads which are the outgrowths of protoplasmic masses, termed nerve cells, situated in the grey matter of the central nervous system. The central end of a divided nerve remains healthy, or approximately so. The other segment, which is called the peripheral end, consists of nerve fibres also, but after division they soon lose their power of responding to stimuli and of conducting nerve impulses. They simultaneously undergo a degenerative change, which can be easily recognised by the microscope, and ultimately atrophy. These fibres having been cut off from the nerve cells—of which they are outgrowths—are no longer capable of receiving that nutritive control which it is the special object of these protoplasmic masses to accomplish. This was first pointed out by the elder Waller, and the term "Wallerian degeneration," by which it is known, is a permanent record of this historical fact.

Even the most rapid suturing of the divided ends together is ineffective to prevent Wallerian degeneration from occurring in the distal segment.

This shows the difficulties attendant on the process of nerve regeneration; for the new fibres have not only to bridge a gap, but they are also necessary to replace the degenerated fibres in the peripheral segment right down to its ultimate and final ramifications in skin, muscles, or other organs.

In the elucidation of the problem as to how this is accomplished, experiments upon animals have been rendered necessary, so as to extend and complete the imperfect information, which is all that can be obtained by clinical observation in man.

But in order to pave the way to this, it is first necessary to allude to the way in which nerve fibres find their way to the periphery from the central nervous system in the embryo. The central nervous system (brain and spinal cord) is originally formed by an infolding from the surface of the most external embryonic layer known as the epiblast, the remainder of the epiblast appearing in the fully formed animal as the epidermis. This infolding is cut off from the surface

epiblast, and an island tube of epiblast is converted by thickening of its walls into the brain in front and spinal cord behind. Its walls contain numerous masses of protoplasm, or primitive nerve cells, which are called neuroblasts. At first these cells have no processes, but branching projections grow out from each; these interlace with the similar processes of other cells, and so bring neighbouring cells, and even distant cells, into communication with each other, to ensure harmonious or co-ordinate action between them. But these branching processes or dendrons are not the only outgrowths of the nerve cell, nor are they the first to make their appearance. The first outgrowth to appear is stouter than those that follow; it grows to the greater distance; it leaves the central nervous system altogether, and ultimately penetrates to peripheral structures. It is known as the axon, and, with few exceptions, every cell body has only one axon. It ultimately becomes the axial conducting core of a nerve fibre, and a collection of these fibres constitutes the bundle known as a nerve. At first the axon is naked throughout its entire length, but later in development it becomes sheathed. The sheaths of the axon are certainly important for its nutrition, and possibly insulate the axon, much as a telegraph wire is insulated from its fellows by a silk or gutta-percha covering. In the fully formed nerve each fibre then consists of an axon or axis cylinder; outside of this is a thick white sheath, which contains complex phosphorised fats—this is known as the medullary sheath or white substance of Schwann; outside of this is a delicate nucleated membrane called the primitive sheath of Schwann, or more usually the neurilemma. Certain new fibres, however, never receive a fatty sheath, and are consequently called non-medullated; these are the fibres which supply the involuntary muscular fibres of the internal organs of the body.

This view, that each nerve fibre develops as an independent outgrowth from a nerve cell, and grows distalwards, finally becoming united to other tissues (*e.g.* muscle fibres) in the periphery of the body, is associated especially with the name of His, and has been accepted by the majority of embryologists.

There have been other views held, but it will be sufficient here to mention only one of these; for it is the one which, next to that of His, has been favoured by investigators. Briefly it is as follows: The nerve fibre is not a secondarily formed

bridge between the central nervous system and the peripheral organs, but exists from the very first, and in subsequent development it merely undergoes elaboration, and increases in bulk and in length as the distance from the central nervous system and the periphery increases with the increasing size of the developing animal.

I shall not fully discuss the pros and cons of this controversy, but only say that the available evidence appears to me strongly in favour of the first of the two views, and it has within the last few months been supported by a very remarkable ocular demonstration of its truth. Mr. Ross Harrison has, in the Johns Hopkins University, Baltimore, actually seen the fibres growing outwards in embryonic structures. Pieces of the primitive nervous tube which forms the central nervous system were removed from frog embryos, and kept alive in a drop of lymph for a considerable time; the cilia of the neighbouring epidermic cells remained active for a week or more; embryonic mesoblastic cells in the vicinity were seen to become transformed into striated muscular fibres, and there was therefore no doubt that even under artificial conditions of this kind—rendered necessary for microscopic purposes—life and growth were continuing. From the primitive nervous tissue, and from this alone, nerve fibres were observed growing and extending into the surrounding parts. Each fibre shows faint fibrillation, but its most remarkable feature is its enlarged end, which exhibits a continual change of form. This amœboid movement is very active, and it results in drawing out and lengthening the fibre to which it is attached, and the length of the fibre increases at the rate of about one micro-millimetre in one or two minutes.

I think these observations show beyond question that the nerve fibre develops by the overflowing of protoplasm from the central cells, and thus give us direct evidence in favour of the view which most embryologists previously held mainly as the result of circumstantial evidence. Such, then, being the general state of our knowledge regarding the way in which nerve fibres grow in the developing animal, it is not surprising to find that the prevalent idea regarding their regeneration after injury follows the same lines. The original teaching of the elder Waller (1852) that regeneration occurs by fibres growing out from the central stump into the peripheral segment of the nerve

was formulated at a time when the relationship of nerve fibres to nerve cells was not so fully recognised as it is at present; and the Wallerian doctrine may be accepted with confidence to-day. It has, however, been questioned from time to time, and the earliest to hold an opposite view was Vulpian. Vulpian, working with Philippeaux, cut nerves in young animals, excising long portions so as to prevent the two ends uniting. Some months later they were surprised to find that new perfectly formed nerve fibres had appeared in the peripheral segment, and that this segment possessed the physiological properties of being excitable and capable of conducting nerve impulses. To this phenomenon they gave the name of "autogenetic regeneration." The publication of these results provoked a long controversy, which lasted from 1859 to 1874, and was closed at the latter date by Vulpian withdrawing his new idea. He did so because in the meanwhile he had repeated his experiments more carefully, and so discovered that, although the ends of the divided nerve had not joined up, connection with the central nervous system had nevertheless been re-established by means of fibres growing into the peripheral segment from other nerves cut through in skin and muscle in the course of the operation.

The controversy has been revived within the last few years, and the position of the disputants has been almost exactly the same as that occupied by Waller and Vulpian half a century ago. Modern investigators have, however, the advantage of being able to apply new methods of research, and are provided with many histological reagents of which the older workers were destitute. It is, however, never safe to argue entirely from microscopic appearances, for nerve fibres may be simulated by non-nervous structures, and a strand that looks like a nerve fibre is not really such unless it can be experimentally shown to be both excitable and capable of conducting nerve impulses.

Vulpian's old doctrine of auto-regeneration has been revived in this country by Ballance and Purves Stewart, and in Scotland by Kennedy. The most prominent and persistent supporter of the autogenetic theory is, however, a German neurologist named Bethe. But none of these investigators have excluded the fallacy which underlay the work of Vulpian and Philippeaux, as has been recently pointed out by Langley and Anderson. These two workers at first thought they also had obtained evidence of purely peripheral regeneration, and it was not until

they carried out careful dissections that they convinced themselves that union with the central nervous system had occurred. The new nerve fibres which grow into the peripheral segment from other nerves divided in the operation, often do so by a devious and contorted course. If the number of medullated nerve fibres in the peripheral end is small, then the connection with central fibres was found to be slight; and in cases where no connection occurred then medullated nerve fibres were entirely absent. Bethe admits a variability in the number of medullated fibres, and this, though easily explicable on the view that such fibres come by accident from the central ends of divided nerves, is not accounted for at all by the autogenetic theory.

Another admission which Bethe makes also weakens his view. He admits that auto-regeneration does not occur in adult animals. He does not, however, state at what age animals lose their power of auto-regeneration, nor explain how it is that after a certain date an animal repairs a divided nerve in the exactly contrary manner to that it would have adopted if the nerve had been cut before that date. The difference which exists between young and adult animals is quite easily accounted for in accordance with Wallerian views; it is simply due to the greater ease with which reunion with central nerves occurs in young and actively growing animals.

Bethe's views have been contested not only by Langley and Anderson, but also by Lugaro, by Kölliker, by Cajal, by Marinesco, by Mott, and Edmunds in conjunction with myself, and by numerous others.

I may mention a few of the experimental results which have come out of the renewed work elicited by the promulgation of the autogenetic theory.

(1) It is possible entirely to prevent reunion with the central ends of divided nerves. In our own work we accomplished this by removing a long stretch of the main nerve experimented with, by making the skin incision as small as possible, and by inclosing the top end of the peripheral segment in a cap of sterilised gutta-percha. Under such circumstances no auto-regeneration occurs.

(2) Pieces of nerve may be transplanted under the skin, and in time a few fully formed medullated fibres appear within the degenerated bundle of fibres. This is adduced by Kennedy as undoubted evidence of auto-genesis, but, again, is easily

explicable on the hypothesis that the new fibres had wandered in from cutaneous nerves divided in the course of the operation, and we showed that if this fallacy is excluded by transplanting the nerve, not into the subcutaneous tissues, but on to the stomach wall in a sheath of peritoneum, no regeneration occurs at all.

(3) The late appearance of the medullary sheath in those portions of the regenerating fibres which are most distant from the place where the nerve is originally cut and sutured, is a conclusive piece of evidence that the new nerve fibres grew from the central end in a peripheral direction.

(4) After regeneration has occurred, the nerve may be again cut across, either on the central side of the original point of section (as in Langley and Anderson's work), or on the peripheral side of the original seat of operation (as in our own work). In the former case Wallerian degeneration occurs in all the new fibres, showing that they were all under the nutritive control of the cells of the central nervous system. In the latter case the degeneration took place solely on the peripheral side of the second cut. The direction of degeneration is always the direction of growth, so this experiment shows that the growth of the new fibres had not started from the periphery centralwards, but in the reverse direction. On looking up the literature of the subject, I found that Vulpian also did this experiment with the same result, and it can hardly be doubted that this formed one of the factors that later led him to abandon the autogenetic theory. An experiment on somewhat the same lines has been carried out recently by Lugaro : he has shown that regeneration of the cut nerves connected with the lower part of the spinal cord does not occur after that part of the spinal cord has been extirpated. This is a very striking piece of evidence, showing the dependence of the growth of fibres on the activity of the cells of the central nervous system with which they are originally connected. Ocular evidence is, however, perhaps more convincing than the description of experimental results, so I will next present to the readers of Science Progress drawings of some of the microscopic specimens prepared by the latest improved methods.

Cajal, by the help of his new silver method, comes to the conclusion that the new formation of nerve axons in the peripheral stump is exclusively due to growth from the central end.

He figures the long and often contorted course of these growing fibres in the swelling at the cut central end, and shows that they ultimately reach their goal—the peripheral segment—in

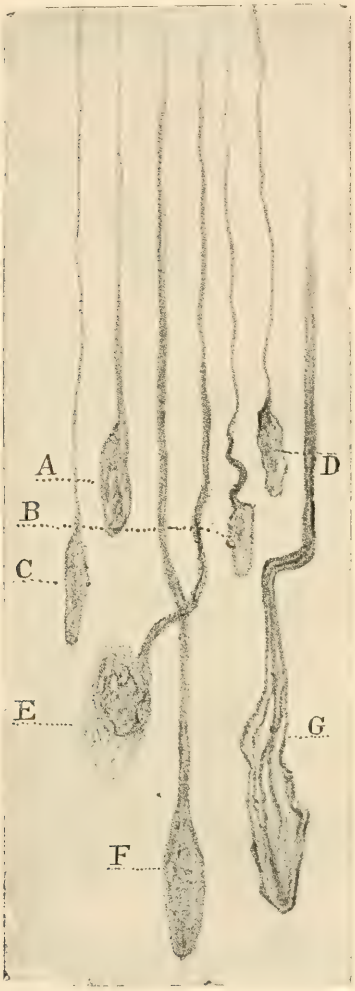


Fig. 1.—Olive-shaped swellings at the ends of nerve fibres growing distalwards from the central ends twenty-one days after the nerve had been divided. (Marinesco.)

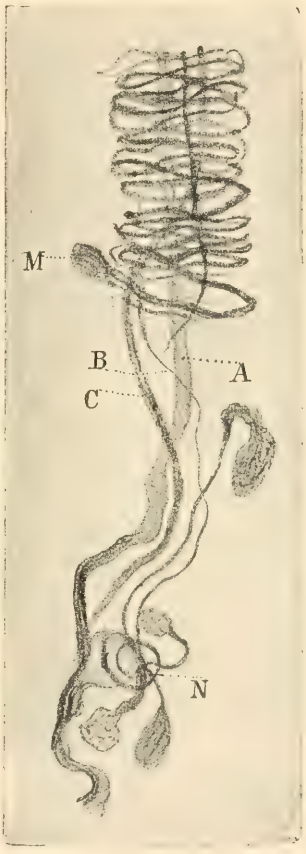


Fig. 2.—Spiral forms often seen in regenerating nerve fibres: the fibres are seen to be of varying thickness, and each is provided with a terminal swelling. (Marinesco.)

time and in spite of all hindrances. The greater the obstacles interposed the later does the union and consequent regeneration in the peripheral end occur. He also draws attention to the

olive-shaped swelling at the free end of each growing axis-cylinder. These are also figured by Marinesco, and I am indebted to the kindness of Prof. Marinesco for figures 1 and 2, which illustrate these swellings; in figure 2 the convoluted course of the new fibres, which is so frequently seen, is shown.

Marinesco calls attention also to the fact that these terminal swellings, although they may roughly be described as olive-shaped, vary a good deal in external form; this is shown in the drawings, and is quite intelligible now that we have Ross Harrison's description of the constant changes of form they exhibit in embryonic history. In regenerating fibres we have not direct evidence that similar amœboid movements take place, for the preparations were made not while the fibres possessed vitality but after fixation with a suitable hardening reagent. Still, the mere fact that they are fixed in various shapes is conclusive evidence that they do exhibit these changing outlines.

Marinesco has passed through the stage so often seen in those who have attacked the problem of nerve repair. In his earlier publications he thought his preparations afforded evidence of auto-regeneration, though he never went as far as Bethe has done in that direction. In his latest papers he has entirely recanted these views, and is now convinced that auto-regeneration is a myth. I reproduce two more of his very beautiful illustrations. The preparations were stained by Cajal's new method, and they require but little comment.

They show the new fibres penetrating the cicatricial tissue of the junction from the central end in a peripheral direction; they show the absence of any new axons developed auto-genetically in the peripheral end. Such preparations ought to carry conviction to those who have any lingering belief in auto-regeneration, that the Wallerian view is the only possible one to adopt.

It must not, however, be supposed that the peripheral end is entirely inactive; for while degeneration is progressing in the axons and their fatty sheath, an active multiplication of the cells of the primitive sheath or neurilemma is taking place. These neurilemmal cells probably play a nutritive action towards the more important structures within them, and Graham Kerr, in a recent study of nerve growth in the fish *Lepidosiren*,

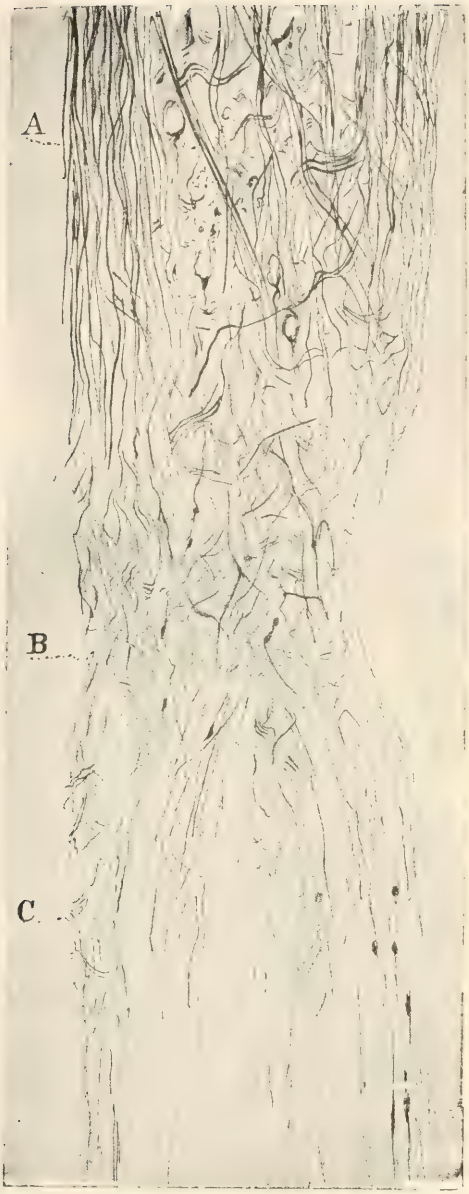


Fig. 3.—Longitudinal section of sciatic nerve of new-born dog eight days after the nerve had been divided. Union had already taken place. At the extremity of the central end (A) growing fibres are seen running in various directions towards the cicatrix (B); C is the peripheral end, into which a few fibres are already penetrating. (Marinesco.)

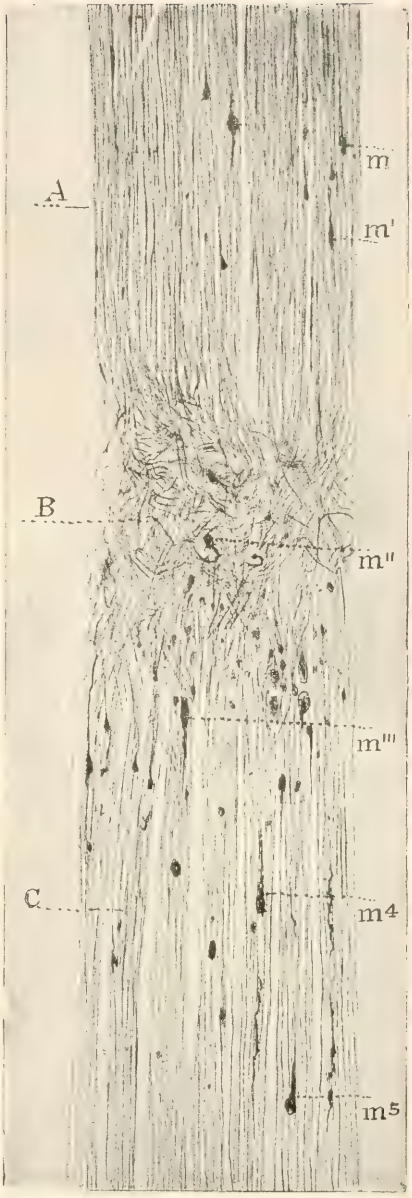


Fig. 4.—Longitudinal section of dog's nerve, twenty-one days after the nerve had been divided. A more advanced condition is seen than that shown in fig. 3. A is the central end; B the cicatrix of union, where the nerve fibres are seen in great numbers taking an irregular course. Into C, the peripheral end, many fibres have already successfully penetrated; m, m', m'', etc., are the terminal swellings of fibres growing from the central stump and directed towards the periphery, except in the case of m'', where the twisting of the new fibre in its efforts to grow had, at the time when the animal was killed, directed the termination backwards. (Marinesco.)

has supported in a very conclusive and entirely independent way the view that Mott and I advanced some years ago of the value of the neurilemma in maintaining the nutrition of the axis cylinder. There is but little doubt also that these cells act as phagocytes in the removal of the degenerated products of the other portions of the nerve fibre. But after this is accomplished they elongate and unite into long chains. It is this appearance that has led some observers into regarding them as true nerve fibres; they have jumped to the conclusion that the neurilemmal cells are also able to form a conducting core, and so have regarded auto-regeneration as a histological possibility. But all recent observations by the best methods, as I have already stated, have failed to discover either an axial core or a fatty sheath in these "embryonic fibres" as they have been termed. Howell and Huber put it very well nearly twenty years ago when they said the peripheral structures are able to prepare the scaffolding, but the axon, the essential conducting core of the fibre, has an exclusively central origin.

The change in the neurilemmal cells which occurs in the peripheral segment is even more vigorous at the central termination of the cut nerve; here its nutritive function (or apotrophic function, as Marinesco calls it) is effective, and provides for the nourishment of the actively lengthening axis cylinders. At the peripheral end, unless the axons reach it, it is ineffective in so far as any real new formation of nerve fibres is concerned. If, however, the axons reach the peripheral segment, the work of the neurilemmal cells has not been useless, for they provide the supporting and nutritive elements necessary for their continued and successful growth. Moreover, the neurilemmal activity appears to be essential. In the white fibres of the central nervous system the neurilemma is absent; in this situation not only is the removal of the products of degeneration a very slow process, but, as I have previously mentioned, regeneration does not occur.

Having now considered the manner in which nerve regeneration occurs as elucidated by experiments upon animals, we can next pass to a study of the problem in man. When the accident is a slight one, or when a surgeon during an operation necessarily divides a number of small cutaneous and similar nerves, the process of repair may be confidently left to nature. But when a large nerve trunk is divided, the case is a different

one—for a large nerve on division curls up at the end, forming a contorted leash of fibres; it also retracts, and a considerable amount of scar tissue is formed. This cicatricial tissue, by the time the nerve has begun to regenerate, has become very dense, and so an impediment to the successful growth of the nerve fibres is interposed. Still, in spite of such a barrier, spontaneous restoration frequently takes place. If the cut were made by a dirty piece of sharp machinery, inflammation usually comes in as a complication, and causes still further delay. In animals, where the cut is made with a clean knife, and antiseptic precautions are employed, this danger is reduced to a minimum, the amount of scar tissue is less, and union may be anticipated without suture. But even here suture hastens recovery, and in man thorough cleansing of the wound and the union of the divided nerve by appropriate ligatures should always be carried out. The growing nerve fibres will then not be left to themselves to find their way into the peripheral end, but will be guided more rapidly to their destination. In a number of cases where the carelessness of the patient has caused him to neglect obtaining this surgical assistance, it may be years before restoration of function takes place, but even under these circumstances the surgeon can help him. The old wound is opened up, the swollen lumps at the ends of the two segments of nerve are removed, and the two ends can then be united; the operation is spoken of as "secondary suture," and recovery is then comparatively rapid.

In some cases where the gap is a long one, some surgeons have been in the habit of transplanting a piece of nerve obtained in a living condition from a recently killed animal to bridge across the interval. This, however, is not to be recommended, since Marinesco has shown that if a transplanted nerve is obtained from another species of animal it is completely necrosed, just as the blood corpuscles of one animal are destroyed by the body fluids of another. The interposition of a foreign piece of nerve is thus in man rather a hindrance than a help.

Many surgeons have been steadfast upholders of the autogenetic theory because they have found in man that sensation may return very rapidly after freshening up and suturing together the ends of a nerve which had been divided a long time previously. They argue that during this time new nerve fibres

must have been produced in the peripheral segment, which would be ready to exercise their functions directly they are placed in continuity with the fibres of the central end.

Examination of these cases shows, however, that sometimes the conclusion has been a hasty one, depending largely on the evidence of the patients themselves, in whom the wish is father to the thought. There was a case of this kind recently in King's College Hospital. Very shortly after the operation the patient stated he was able to feel, but these sensations rapidly subsided, and sensation did not really return until months later. The preliminary sensations were doubtless subjective; the irritation of the nerve in the scar lasted some hours, and the sensations so produced were referred by the patient's mind to the original terminals of the fibres.

In other cases the genuineness of the early recovery is doubtful, because insufficient care is taken in testing the patient's sensations. In spite of sensitiveness to such tests as needle pricks, there is usually absolute anæsthesia to the far more delicate test of stroking the hairs over the affected region until quite late dates. Head and Sherren have recorded a large number of surgical cases, but evidence of early recovery is usually lacking; there is some difficulty in localising the stimulus so that it should not affect the hyperæsthetic marginal zone of the anæsthetic region, and if this danger is recognised it can be avoided. Another pitfall is this: the deep sensibility of the subjacent parts, such as would be excited by needle pricks, or by pressure, is entirely independent of cutaneous sensation. The fibres subserving this form of sensation run mainly with the motor nerves, and are not destroyed by division of all the nerves to the skin. Neglect to recognise this fact will explain some of the results of those who have published cases of early recovery.

The difficulty of clinical observation on others induced Dr. Head to combine with his experiments on animals and his observations on patients, an experiment on one of the sensory nerves of his own arm. This gave an opportunity for the study of the phenomena by a trained observer upon himself. He certainly experienced no early return of function, and the date at which sensation did come back coincides closely with the dates obtained in animals by physiologists for the reappearance of new and fully formed nerve fibres.

In the course of this work he made the interesting dis-

covery that the first kind of sensation to return is of a vague nature, which he terms *protopathic*; he associates this with the activity of the fine medullated fibres which replace the degenerated ones at an early date; return of protopathic sensibility begins about the eightieth day. The more elaborate sensations and power to localise them accurately return much later, and this *epicritic sensibility*, as Head terms it, is usually not perfect until months, or even years, have elapsed after the regeneration started.

By this time, as was shown by experiments on animals, the fine nerve fibres which subserve protopathic sensation are largely admixed with a later growth of larger nerve fibres, and he believes that epicritic sensation is subserved by these. He also postulates that the three kinds of sensation (deep, protopathic, and epicritic) are related to different kinds of end-organs in the peripheral structures.

Granting that earlier observers had been led into errors by not being acquainted with Head's discoveries, and that many cases of supposed early recovery can be explained in the manner already indicated, there remains a small residuum of cases in which such explanations do not hold, and in which early recovery appears to have been an undoubted fact. Of these, I would particularly refer to some cases recorded by Dr. Kennedy of Glasgow, in which the return of sensation of some sort, especially to painful stimuli, was a matter of only a few days. In these cases due care appears to have been taken to exclude any bias of the patient's own mind. He admits that such cases are rare; from his own point of view auto-regeneration would therefore appear to be an unusual phenomenon. Granting that the early recovery was genuine, it seems to me there is a much more probable explanation than that of auto-regeneration. They are doubtless instances where extremely rapid growth of new axis cylinders from the central into the peripheral segment of the nerve took place. Dr. Kennedy's cases appear to be happy examples of the date of the secondary suture being such that the usual impediments to repair were minimal. The preparatory work of the neurilemmal cells in the distal portion of the nerve had evidently reached that stage when they were most fitted to receive the new axis cylinders, and by their metabolic activity favour the onward growth of the fibrils at a rapid rate. The examination of

Dr. Kennedy's own records supports the same view. In three of his four cases sensation returned first in the parts nearest the suture, and later in more distant parts, such as the finger tips. This surely proves that regeneration was occurring in a peripheral direction. The record of the fourth case gives no details of the order of recovery. The only difficulty remaining is the unusual rapidity of the reparative process. I say "unusual" because most of our ideas of the rate at which axis cylinders grow are derived from cases in which gross impediments to growth are present. I have, however, been struck in some of our own observations with the rapidity with which the central unites with the peripheral end, even when an inch or more of nerve has been excised. In some cases there was a well-defined strand of union after a few days. This is especially the case when young and vigorous animals are employed. In two of Dr. Kennedy's cases, the patients were in the prime of life (aged twenty-nine and thirty-seven respectively); the other two were children—aged six and sixteen respectively.

The introduction of the new methods of Cajal has now furnished us with a method of tracking the growing axis cylinders with a certainty which was previously lacking; and Marinesco, availing himself of these methods, has shown that the lengthening of the regenerating fibres is demonstrable twenty-four hours after a nerve has been cut.

This concludes what I have to say on an important problem of what we may call applied physiology. In the present state of our knowledge it is impossible to avoid controversial questions. The proverbial disagreement between doctors is specially true of physiologists, and really this is only as it ought to be. Whilst knowledge is in the making there must be divergencies of opinion, and it is only by a full and free discussion of these, and by the renewed research of which criticism is the stimulus, that any certainty in the way of truth can be arrived at.

MENDELISM

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Perhaps the most interesting, certainly the most sensational, chapter in the history of biology, when it comes to be written, will be that which deals with the discovery of Mendel's papers and with the fruit which that discovery has borne. We are already in possession of all the material for the former topic; and the first instalment of the fruit which has already been harvested augurs well for the quality of what is to come.

In 1865, a man absolutely unknown to the biological world, Gregor Johann Mendel, read before a meeting of the Natural History Society of Brünn a paper on his experiments with Peas, entitled "Experiments with Plant Hybrids." To-day no name is better known to biologists than that of Mendel. And yet, when he died in 1884, he was as obscure as when he read his famous paper. Indeed, it was not until sixteen years after his death that Mendel suddenly burst from obscurity into fame.

In 1900 Mendel's experiments with Peas were repeated, and his results confirmed, independently by De Vries in Amsterdam, Correns in Leipzig, and Tschermak in Vienna. This spark—the discovery of Mendel's paper—has been responsible for the generation of an enormous amount of energy, which has manifested itself ever since in a continually smouldering train of investigation; and on one or two occasions in explosions of controversial violence.

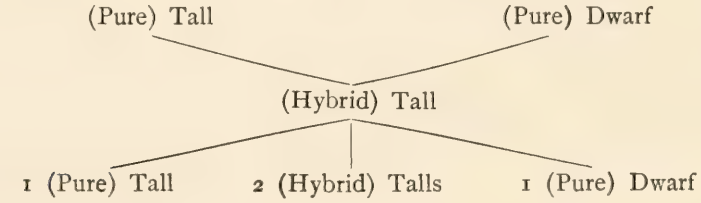
We must now make it our business to become familiar with the facts which Mendel discovered, and with the interpretation which he put upon them. Mendel found that varieties of the culinary pea, *Pisum sativum*, could be classified according to a number of constant, true-breeding characteristics, such as the form of the plant, whether normal (*i.e.* tall) or dwarf; or such as the colour of the cotyledons of the seeds, whether yellow or green; and so forth.

Mendel crossed a Tall with a Dwarf. The resulting hybrid

was invariably a Tall. Tallness, therefore, he called the *dominant* character and dwarfness the *recessive.*

These hybrids were allowed to self-fertilise (the normal process in *Pisum*), and seeds gathered from them gave, when grown, 1064 plants, of which 787 were tall and 277 dwarf; that is to say, the hybrid Talls produced Talls and Dwarfs in the proportion of 2·84 to 1, or roughly 3 to 1.

The seeds of these plants were sown, and it was found that all the Dwarfs bred true, whilst of every three Talls, one produced only Talls, the other two giving rise to Talls and Dwarfs in the proportion 3 to 1. The foregoing account may be summarised in the following diagram:



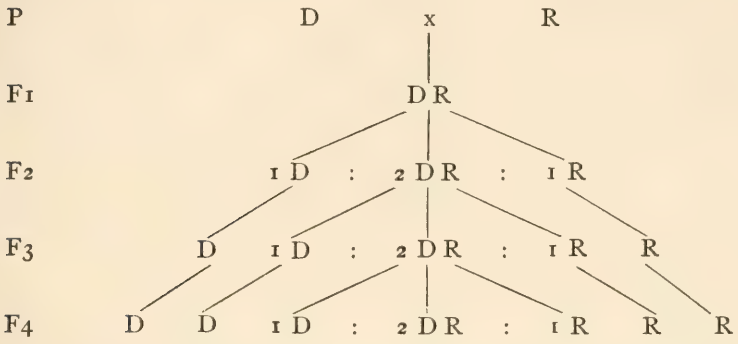
Let us now look at the three kinds of Peas which compose the generation in which Pure Talls, Hybrid Talls, and Pure Dwarfs appear in the proportion 1 : 2 : 1. We already know that all the Dwarfs breed true, that a third of the Talls breed true, whilst the rest of the Talls produce Talls and Dwarfs in the proportion 3 to 1. This proportion—3 to 1—is made up in the same way as the same proportion in the preceding generation—namely, 1 Pure Tall; 2 Hybrid Talls; and 1 Pure Dwarf. All these Dwarfs breed true; all the Pure Talls breed true; and the Hybrid Talls produce Talls and Dwarfs in the proportion 3 to 1. And so on.

There are two sets of symbols which are very convenient in describing these phenomena.

The first set describes the different kinds of individuals; the second the generations. D denotes the dominant form (in the case we have been discussing, the Tall), R the recessive (the Dwarf), and D R the hybrid.

P denotes the parental generation; F1, the result of crossing the two parent forms—in our case, the Hybrid Tall; F2 denotes the next generation, *i.e.* that in which the dwarfs reappear in the proportion 25 per cent.

We may now summarise the Mendelian phenomenon in the following diagram:



What is the cause of this beautifully regular and definite phenomenon? Mendel answered the question in this ingenious way. He believed that the germ-cell of the hybrid pea did not represent a mixture of tallness and dwarfness, but that a germ-cell represented *either* a tall *or* a dwarf, and, moreover, that half of the germ-cells represented tall and half of them dwarfs. Let us see what is the result of the union of—say—a hundred male germ-cells, or pollen-cells, with a hundred female germ-cells, or egg-cells. Before we proceed, let us make certain of two points which are essential to the argument. Mendel believed that a pure-breeding tall pea contained only tall-representing germ-cells—in fact, that the reason that it bred true was that it did contain them; and that the dwarf contained only dwarf-representing germ-cells. Mendel had also found that the result of a union between a "tall" germ-cell and a "dwarf" one was a hybrid which bore the tall character. Now let us return to our argument.

Fifty of the hundred pollen-cells would be "tall," and fifty "dwarf." Let us consider the "talls" first. As half of the eggs-cells are "tall" and half "dwarf," the "tall" pollen-cell has an equal chance of meeting a "tall" and a "dwarf" egg-cell. So that twenty-five of the "tall" pollen-cells would meet "tall" egg-cells, and twenty-five would meet "dwarf" ones; and the resulting unions would be (writing T for Tall, and D for Dwarf):

25 T T
25 T D

Similarly twenty-five of the fifty "dwarf" egg-cells would meet "talls" and twenty-five "dwarfs," or briefly:

25 D T
25 D D

The total result therefore is:

25 T T
25 T D
25 D T
25 D D

Now we already know that the result of the union of a "tall" with a "dwarf" germ-cell is a hybrid which is tall, and Mendel found that it made no difference whether the tall character was carried by the male parent and the dwarf by the female, or *vice versa*. So that the above result can be written:

25 T T (Pure Talls)
50 T D (or D T) (Hybrid Talls)
25 D D (Pure Dwarfs)

The result of the random union of two sets of germ-cells, each set consisting of 50 per cent. of germ-cells bearing the Recessive and of 50 per cent. bearing the Dominant character, can be admirably illustrated by drawing one counter at random from a hat containing fifty Red and fifty White counters, and another from another hat with similar contents, and by placing the three kinds of pairs in three separate rows on the table, according as whether they are R W, R R, or W W. The larger the number of trials you make the closer will the approximation to the proportion of 25 R R, 50 R W, 25 W W be. Counters are worse than marbles for illustrating this, by reason of the difficulty of thoroughly shuffling them. But they are better than them, because the phenomenon of dominance and the proportion 3 : 1 can be illustrated with them, the former by merely making it a rule to put the red counter on the top of the white when a red and a white are drawn together, the latter by superposing the upper counter in every pair so carefully that the lower one is invisible. If this is done effectively there will be seen, at any rate from a slight distance, to be 75 per cent. red counters and 25 per cent. white. But if you jog the table the difference between the previously apparently identical reds will be revealed. It is also very

easy to illustrate subsequent results with the counters. The result of mating the hybrids in F2 can be illustrated in exactly the same way as that of mating the F1 hybrids. And it is readily seen that it is no more possible to get anything but Dwarfs from the Dwarfs in F2 than it is possible to get anything but pairs of white counters by drawing from two hats each containing nothing but white ones, and that it is no more possible to get anything but Talls from those Talls, *i.e.* the pure ones, which resulted from the union of like gametes than to get anything but pairs of reds from drawings from two hats containing only reds.

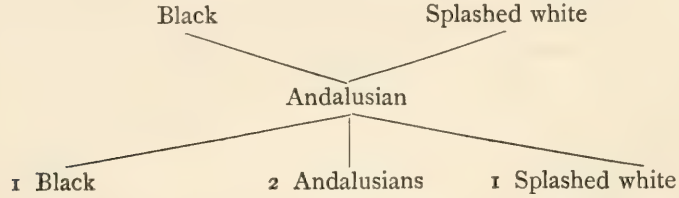
The animal or plant resulting from the union of two germ-cells or gametes—and all animals and plants which reproduce sexually result from such a union—is called a *zygote*; that resulting from the union of like gametes or germ-cells is called a *homozygote*; that from the union of unlike gametes a *heterozygote*.

The heterozygote in the case which we have been considering as an example was only distinguishable from the dominant homozygote by the fact that when allowed to self-fertilise it produced Dwarfs as well as Talls. But sometimes the result of crossing two pure strains is different from either of them—that is to say, the heterozygote has a character peculiar to itself. This makes it possible to distinguish between the heterozygotes and the dominant homozygotes in F2 otherwise than by breeding from them.

The phenomenon may be illustrated by the famous case of the Andalusian fowl. If you buy a pair of these birds from the very best source you will find that they will not breed true, but that they will produce besides the Andalusians blacks and splashed whites, and that on the average these three forms will be produced in the proportion 1 black, 2 Andalusians, 1 splashed white. If you were not acquainted with Mendelian phenomena, but were guided by the principles of heredity which were universally held in pre-Mendelian days (and are still by those who are not Mendelians), you would sell the blacks and whites for eating and breed from the Andalusians, in the belief that, as they at least, to your own personal knowledge, had an Andalusian father and mother, they would be more likely to breed true than a pair of Andalusians of unknown and, as you would expect from the result

of mating them, of mixed parentage. Your anticipation would not be fulfilled. Your Andalusians would again produce blacks, Andalusians, and splashed whites in the proportion 1 : 2 : 1. But if you were acquainted with Mendelian phenomena you would immediately suspect that the Andalusian was a heterozygote form, and that the two homozygote forms which by their union gave rise to it were the blacks and the splashed whites. This is indeed the case. Mate the black with the splashed white, and you get nothing but Andalusians. The obvious plan, therefore, instead of selling the blacks and whites to the poulterer and keeping the Andalusians to breed from, and then only getting 50 per cent. of what you want, is to sell the Andalusians to fanciers, keep the blacks and whites, and get 100 per cent. of Andalusians by crossing them, making occasional matings of Andalusians to keep up the supply of blacks and whites.

This case is summarised in the following diagram :



Let us now return to the Peas. We have referred in detail to only one pair of characters, namely, Tall and Dwarf. Mendel dealt with six other pairs of characters, namely :

1. The shape of the ripe seeds, which was either round or wrinkled.
2. The colour of the ripe cotyledons in the seed, which were either yellow or green.
3. The colour of the seed-coat, which was either white or grey (with or without purple spots).
4. The texture of the ripe pods, which was either hard and inflated or soft and constricted between the seeds.
5. The colour of the unripe pods, which was either green or yellow.
6. The arrangement of the flowers on the stem. The flowers either came off normally at the nodes along the stem, or they were situate in a bunch at the top of the stem ; this latter is the so-called Mummy habit.

The two members of each of these pairs of character stand to one another in the relation of dominant and recessive. In the above list the dominant member of each pair is written first. The two characters which form such a pair are called *allelomorphs*; and green is said to be allelomorphic to—*i.e.* forms the other member of a pair with—yellow. Similarly yellow is allelomorphic to green.

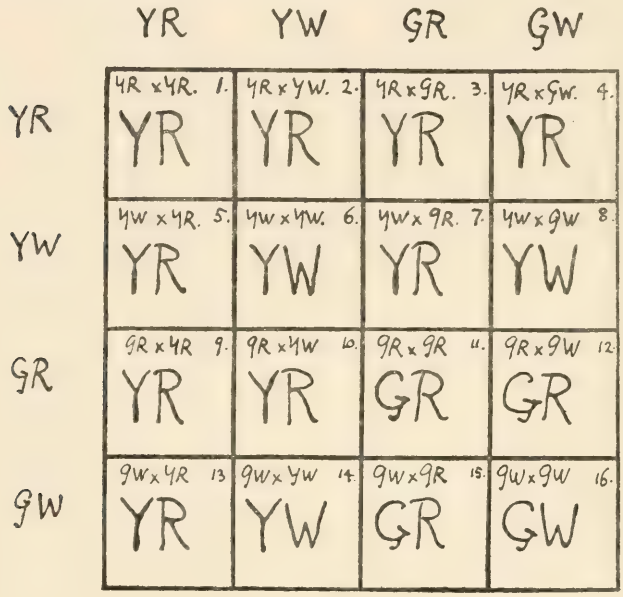
We have so far, in considering the results of crossing an animal or a plant, paid attention only to a single pair of allelomorphs, tall and dwarf, black and splashed white. We must now ask ourselves, What is the relation between character belonging to different allelomorphic pairs? And the answer, broadly speaking, is that in the case of some characters there is no relation, whilst in the case of others there is; or, to amplify the answer, in the case of some characters the members of distinct allelomorphic pairs exercise a very definite effect on one another, whilst in the case of others they are entirely independent of one another. We will deal with the latter case first, because it is simpler.

What the result of mating a green round with a yellow wrinkled pea will be, can be answered by reference to the table of characteristics on p. 434, in which (it will be remembered) the dominant member of a pair is written first. The result will be a yellow round one. What the result of allowing these to self-fertilise will be can be predicted from the result of making drawings of two counters from each of two hats, which contain equal numbers of green and yellow, red and white counters.

The number and nature of the possible combinations is given by the number and contents of the squares in the Table on p. 436.

Y and G stand both for yellow and green counters and "yellow" and "green" germ-cells; R and W stand both for red and white counters and "round" and "wrinkled" germ-cells. The four pairs of letters along the top of the table represent the four kinds of male gametes; the pairs along the side the four kinds of female ones; the squares represent zygotes. Let us consider the results of their union, beginning at the top left-hand square. (In the following account Y is to be read as yellow, G as green, R as round, and W as wrinkled.) Here we have to do with union between two Y R gametes. The result is a pure Y R zygote. In the square to the right of

it, it is a case of a union between a Y R egg-cell and a Y W pollen-cell; the result is a Y R zygote, which is a homozygote regards colour and a heterozygote as regards shape. In the next square to the right a Y R gamete meets a G R gamete; the result is again a Y R zygote, which differs from the last in that it is homozygote as regards shape and heterozygote as regards colour. In the last square on the top line a Y R gamete meets a G W one; the result is a Y R which differs from any of the preceding ones by being heterozygote both as regards



colour and shape. And so on throughout the table. The nature of the sixteen possible kinds of unions of gametes is written in small letters in the sixteen squares of the table. The characters of the resulting zygotes are written in large letters. When this explanation is being illustrated with counters, the nature of the zygote in each case is given by making it a rule always to put a yellow on the top of a green counter and a red on the top of a white.

The result therefore of allowing our Y R hybrid (produced by Y W and G R) to self-fertilise should be:

9 Yellow round (squares 1, 2, 3, 4, 5, 7, 9, 10, and 13).

3 Yellow wrinkled (squares 6, 8, and 14).

3 Green round (squares 11, 12, and 15).
5 Green wrinkled (square 16).

Or, briefly, 9 Y R, 3 Y W, 3 G R, 1 G W in every sixteen peas.

Of the 9 Y R, only 1 (square 1) is homozygous in both respects, and should produce only Y Rs. Two Y Rs are homozygous in colour only, but heterozygous in shape (viz. squares 2 and 5); they should produce only yellow, but both "Rounds" and "Wrinkleds." Two Y Rs are homozygous in shape, but heterozygous in colour (viz. squares 3 and 9); they should produce only rounds, but both "Yellows" and "Greens." The remaining 4 (squares 4, 7, 10, and 13) are heterozygous both in colour and in shape, and should produce all 4 kinds—Y R, Y W, G R, and G W.

On the 3 Y W, 1 (square 6) is homozygous in both shape and colour, whilst the remaining 2 (squares 8 and 14) are homozygous in shape only. Similarly with the 3 G Rs, that in square 11 is homozygous in both respects, the other 2 (squares 12 and 15) being homozygous in colour only. It will, of course, be noted that the character in respect of which all the 3 Y Ws and all the 3 G Rs are homozygous is a recessive one—namely, wrinkledness in Y W and greenness in G R.

There is only 1 G W zygote which, since both its characters are recessive, is therefore homozygous in both respects.

A very close approximation to the result 9 Y R, 3 Y W, 3 G R, 1 G W has been obtained in experiments by Mendel, Bateson, Hurst, and myself. And the various types of Y R, Y W, and G R have also been recognised.

Another point of view from which the proportion 9 : 3 : 3 : 1 may be regarded is from that of the zygotes solely. If we have a generation which displays the two characters of one pair Y and G in the proportion 3 Y to 1 G in every 4, and the two characters of another pair R and W in the proportion 3 R to 1 W in every 4, and if we further suppose that the two pairs are independent of one another, we should expect that in every 16 (= 4 × 4), 9 (= 3 × 3) would be Y and R, 3 (= 3 × 1) Y and W, 3 (= 3 × 1) G and R, and 1 (= 1 × 1) G and W. And we find that this is so, which shows that the two pairs are independent of one another.

Having become familiar with the signification of the 9 : 3 : 3 : 1 proportion, let us proceed to the discussion of other results which can only be interpreted in the light of it. We need not

leave the Pea for illustration. If we ask a corn-dealer for a pennyworth of Maple or Partridge Peas, he will give us a kind of pea the seed-coat of which at first glance appears a uniform brown, but on closer inspection is seen to have a ground-colour of a pale brown, on which is a very beautiful mottling, consisting of anastomosing tracts of a rich brown colour. This type of coloration is called mapling. Another type of coloration is that which is often seen on (though it is not necessarily associated with) the kind of pea which is much grown and eaten on the Continent, and is known as the Sugar Pea. In this type of coloration there are minute spots (discernible by the naked eye) of slightly varying sizes and of a rich purple colour on a greenish grey background. The former type will be referred to as "maple" and the latter as "purple spot."

When a pea with a maple seed-coat is crossed with one with a purple spotted coat, the result is a pea on whose seed-coat both mapling and purple spots exist. This suggests that maple and purple-spot are not allelomorphic to one another, but belong to separate pairs which are supposed to be maple (M) and not-maple (nM), and purple spot (P) and not-purple spot (nP). This sounds very much like a logical exercise, a matter of words and not of things. But the reality of it is shown by breeding from the hybrids; for by doing this we actually get peas, which we can touch and see, which exhibit neither mapling nor purple spotting. We get, in fact, the following four types of peas in the proportions given by the numbers which precede them:

9 M P, 3 M, 3 P, 1 grey.

If we write this in a form analogous to—

9 Y R, 3 Y W, 3 G R, G W—

we should have:

9 M P, 3 M nP, 3 P nM, 1 nP nM.

The nP nM is grey because all these colours are on a background of pale grey. This proportion shows that we are dealing with two independent pairs of characters, viz.:

1. Maple and not-maple.
2. Purple spot and not-purple spot.

Now we come to those cases in which one of the characters

of a pair of allelomorphs is not independent of a character in another pair.

We will cross a pea with a pale grey seed-coat, such as that which formed the background for the purple and the maple (many field peas exhibit no more than this grey colour), with a pea with no colour at all in its seed-coat, as is the case in a great number of the peas grown for the table. The result is a grey-seeded pea *on which there are purple spots*, which existed in neither parent. Heretofore this would have been labelled as an example of reversion and the matter would have been regarded as settled, or at any rate done with. But to call a thing reversion does not make one any wiser about it. Mendelism has provided a reasonable explanation of reversion in this case. Let us see how. The result of breeding from these grey-coated purple-spotted hybrids provided the clue. There were produced 9 grey with purple spots, 3 grey, and 4 white.

What does this mean? The 9 : 3 : 3 : 1 proportion suggests an explanation. It is supposed that here, as in the case of the cross between the maple and the purple spot, we are dealing with two pairs of allelomorphs, namely, (1) grey (G), and not-grey (nG), and (2) purple spot (P) and not-purple spot (nP). The grey pea exhibits the dominant grey character (G) of that pair. The white pea possesses—and here we come to the case of the interdependence of characters in separate pairs—the dominant purple spotting (P) of that pair; *but the purple spotting is not exhibited because one of its properties is that it cannot be manifested unless associated with the grey coat.* Bearing this theory in mind, let us write the 9 : 3 : 3 : 1 scheme for the two pair of allelomorphs G and nG, P and nP. It will be:

9 G P, 3 G nP, 3 P nG, 1 nP nG.

But we see that in the 3 P nG the purple spot is there, but the grey coat is not. Therefore *ex hypothesi* it will not be manifested and these three seeds will appear white, which gives the proportion 9 grey with purple spots, 3 grey and 4 white.

The possession by the hybrid of a character which neither of its parents possesses is accounted for by supposing that that character (in this case purple spotting) depends for its manifestation on two factors (in this case P and G), one of which exists in one parent and the other in the other. This Mendelian hypothesis therefore enables us to account for the reversion and for the

otherwise meaningless proportion 9 : 3 : 4; or perhaps we should not say more than that the facts are consistent with the truth of this theory.

We will now pass from the culinary to the sweet pea, and describe Bateson's beautiful experiment. One of the countless varieties of the sweet pea grown to-day, Emily Henderson, a pure white, is remarkable for the fact that, whereas the pollen grains of most other varieties are cylindrical with almost parallel sides, some plants of it have this ordinary "long" pollen whilst others have *irregularly round pollen.* The irregularity is never so much pronounced that the round pollen can for a moment be mistaken for the long. It may help those familiar with peas and beans to say that the contour of the round pollen is never more irregular than that of the most irregular wrinkled peas, whilst that of the long pollen may be compared to a stout example of the dwarf bean Non Plus Ultra. Bateson crossed the long-pollened form of Emily Henderson with the short. *The result was a sweet pea of a deep purple colour.* The purple of the standard, the single outer erect petal, was of a redder shade than that of the wings, the two petals just below the standard. This sweet pea is known in the fancy as Purple Invincible, but is seen more often now in cottage gardens than in up-to-date collections. Its type of coloration is that of the original sweet pea as first brought into cultivation. The wild *Lathyrus odoratus*—of the Purple Invincible type—is common in Sicily. Here then is an extraordinary case of reversion. Two pure white sweet peas differing merely in the shape of their pollen are crossed, and a hybrid with the coloration of the ancestor of all cultivated sweet peas is the result. When these hybrids are allowed to self-fertilise, there results in F_2 a variety of forms already well known to the fancy. These are: Purple Invincible again, Picotee, Painted Lady, and Tinged White and pure whites. Passing over the proportions in which the various coloured forms appear, there are found to be 9 coloured to 7 white.

Now, the 9 : 3 : 4 proportion in the culinary pea suggested the existence of two pairs of characters, one of which—the purple spot—could not be manifested in the absence of the other, the grey coat; though the grey coat could be manifested in the absence of the purple spot. The 9 : 7 is accounted for by supposing that colour in the sweet pea depends for its existence upon the simultaneous presence of two factors of distinct

allelomorphic pairs, *neither of which* can be manifested in the absence of the other. These factors have been called C and R, their absences c and r respectively. If we write the familiar 9 : 3 : 3 : 1 scheme again, we get

9 C R, 3 cR, 3 Cr, 1 cr.

Only in the 9 C R are both C and R present; in the 3 cR and the 3 Cr only one of them is present, whilst in the 1 cr neither of them is. So that only the 9 are coloured and the remainder are all white.

The actual proportion of purples and reds and whites in F2 in this instance is 27 purple, 9 red, 28 white (= 36 coloured to 28 white, *i.e.* 9 coloured to 7 white). The existence and proportions of these reds are accounted for by calling in a new pair of allelomorphs, B and b. As already stated, colour is due to the meeting of C with R; if B is absent the colour is red, if present it is purple. But we will not deal further with this now.

Having now seen how these complicated cases of segregation, together with two instances of reversion, have been elucidated by Mendelian analysis, let us turn to other groups of the animal and vegetable kingdoms, and see what other characters have been dealt with in this way.

Except for the pair of allelomorphs with which we illustrated the simple Mendelian phenomenon, and for the very superficial reference to roundness and wrinkledness in peas, all the characters we have dealt with so far have been colour characters. But Mendelian inheritance is by no means confined to colour characters, as we shall shortly see. Perhaps one of the most striking instances of this is that studied by von Guaita, Weldon, and myself, the waltzing habit in mice. The waltzing habit characterises a race of mice known as Japanese waltzing mice, which have pink eyes and small patches of fawn on the shoulders and rump. A waltzing mouse does not always waltz, but can always be distinguished immediately from a normal mouse. The waltzing itself consists in merely spinning round and round very swiftly in one spot on all-fours. It is not in the least like waltzing. It is simply running round in a circle sometimes at a very great pace for several minutes at a time, so that all that you can see is a sort of nebulous ring of mouse. They do not always go round in the same direction,but sometimes

in a right-handed direction, sometimes in a left. But when it is not waltzing, a waltzing mouse is immediately recognisable by the appearance of complete lack of control over the movements of its head, which is every now and again thrown back into an apparently very uncomfortable and useless attitude. A waltzing mouse also has the habit of running or rather shuffling backwards, waving his head vigorously from side to side the while. This mouse is said to have come originally from Japan. They certainly exist there now, but I have not been able to obtain any alive from that country. The depth of the ignorance of the general public concerning the simplest facts of heredity is shown by the fact that the following story of the origin of the waltzing mouse has been printed in a daily paper and, presumably, believed. "A mouse fancier once caught the head of one of his pets in the door of his cage. The mouse nearly died, but on recovery exhibited the waltzing movements now so familiar. Wishing to perpetuate the curiosity, the owner of the mouse carefully preserved and bred from the anomaly, and so originated the breed of waltzing mice!" What actually happened was probably that the feature arose as a sport which was carefully preserved and bred from. Waltzing is, in fact, a very good example of the kind of character that can arise in a tame breed, and be preserved because it tickles the fancy of man. Nature does not tolerate curiosities of this kind for a moment, and promptly eliminates them. The abnormality is due, not, as was originally believed, to the absence or atrophy of one of the semicircular canals, which have been demonstrated to be all there, but to a deficiency in their nerve supply. The waltzing is a constant character of the race; the children of waltzing mice mated together being all waltzers.

When such a waltzing mouse is mated with a normal mouse —with an ordinary white mouse, for example—the hybrid obtained is always *normal*, like the white mouse. Waltzing, therefore, is recessive, in the Mendelian sense, to normality of progression. In F_2 we should expect the waltzing to reappear in the proportion of 25 per cent. of the whole fraternity. Reappear it certainly does, but not quite in the proportion expected. The number of waltzers, indeed, falls below 20 per cent., in the many hundreds of F_2 mice which I have raised. I do not think that this deficiency is due to any complication of the process of segregation in the germ-cells,

but believe it is merely due to the greater mortality which almost certainly takes place among waltzing individuals than among normal ones between the time when they are born and the age—from ten days to two weeks—when the characters of the mice are first registered. Waltzers are much more delicate than normal mice; and it is likely that this delicacy is more fatal in youth (perhaps even before birth) than in middle age.

The mice afford an excellent example of reversion. The Japanese waltzing mouse is almost an albino, and would be were it not for the patches of fawn-coloured fur on the shoulders and haunches. It has pink eyes. It was crossed with an albino mouse. The result, where the albino used was a pure-bred one, was a mouse hardly distinguishable at first sight from the common house mouse. A closer inspection reveals the lighter colour of the belly. Their eyes are jet black. And this is the most remarkable feature of the cross —the production of a black-eyed form from two parent forms both of which had pink eyes. These hybrids are not merely wild in their coloration, but are always noticeably healthier, stronger, and wilder than their albino parent, and infinitely more so than their waltzing parent. As already stated, they never waltz. When they are mated together they produce a generation which is composed of the three colour categories we have just mentioned in the proportions indicated by the percentages prefixed to them—viz. 25 per cent. pink eye and coloured coat (that of the Japanese waltzer), 50 per cent. dark eye and coloured coat (that of the hybrid), and 25 per cent. pink eye and colourless coat (*i.e.* complete absence of pigment or albinism.) The distribution of waltzing over these various colour categories is interesting. It is distributed, as it were, at random—that is to say, the waltzing character is not necessarily associated with that colour category with which it was associated in the pure waltzer, but may be associated with any of the three colour categories. So that we get in F_2, besides waltzers coloured like their pure grandparents, waltzers with the black eyes and the grey coat of the house mouse, and albino waltzers. It may be noted in passing that these albino waltzers correspond to the green wrinkled peas we have already discussed—that is to say, they represent the association in F_2 of the recessive character of one parent with the recessive character of the other parent in one individual,

which, since both characters it bears are recessive, may be counted on to breed true. It does.

Another illustration of a character other than colour is that which has been studied by Mr. R. H. Biffen. One of the most disastrous pestilences which affect the wheat is the fungoid pest known as Yellow Rust (*Puccinia glumarum*). Some varieties of wheat are more susceptible to it than others; for example, the variety Michigan Bronze is hardly ever free from it. Another variety grown by Mr. Biffen may be regarded as practically immune, for, although it was grown for four years in close proximity to the most rust-stricken varieties, it was not affected by the disease. This immune variety was crossed with Michigan Bronze. The hybrids were all so badly affected by the disease that one could not find an area an eighth of an inch square unattacked by the rust. No difference in respect of their susceptibility to the disease could be discerned between the hybrid and Michigan Bronze. But the hybrid did differ from it by the fact that whereas the susceptible parent hardly set a grain, the hybrid gave a moderate crop.

"Every available grain was sown in plots alongside the parent varieties, part on land which had been exhausted on a previous crop of wheat, and part on land which had carried a crop of clover the previous season and consequently was in high condition. The difference in cultivation, however, made no difference in the results of the experiment. The rust was late in appearing that season, but again every plant of the susceptible parent was stricken, and all of the immune type escaped entirely. The hybrid plots were badly attacked, and when the epidemic seemed to be well advanced, the plants were sorted into two groups—namely, those which were attacked, and those showing no signs of the disease even on the withering basal leaves. On some plots the diseased plants were cut out, leaving those free from infection for a subsequent examination. A few individuals, which had escaped the attack at the early stage, became infected later, and these were then added to the total of susceptible plants. The statistics showed that 1,609 diseased plants were present and 523 immune, or a ratio of 3·07 : 1. There cannot, I believe, be any question that these latter were really immune, for they were surrounded by plants covered in rust, whose leaves were continually

rubbing against them. Further, if a variety is susceptible, no plant of it under field conditions ever appears to escape."[1]

Mr. Biffen concludes with the following remark: "Of the problems this opens up to the pathologist, nothing need be said here: for the present we are concerned with plant improvement, and it need only be noted that, according to the report of the International Phytological Bureau in 1890, the attacks of rust cost Germany some £20,000,000 sterling. Such figures give one some idea of the stakes the plant-breeder can now play for, and, thanks to the work of Mendel, with the reasonable certainty of winning."

But it is not merely by the discovery of facts of this kind that Mendelism is of service to the breeder of animals and plants.

Mendel and his followers have already put into the hands of breeders general principles of the greatest value. For example, those whose business is to breed cattle or carnations, or whose hobby is to breed fancy mice or sweet peas, and strive to improve their strains by crossing, are likely to be disappointed if they expect anything new in their first crosses. What could be more discouraging than to obtain a house mouse by crossing the delicate little waltzing mouse with the albino? And yet I have raised an entirely new colour—lilac, as it is called—by mating these hybrids together. Similarly in sweet peas the production of the original wild type of that flower by crossing two of the most beautiful modern strains would not tempt one to repeat the experiment. Mendelian principles drive home the lesson that we must expect nothing in the way of novelty from the first generation, and that it is on the next one that we must concentrate our attention.

Another extremely valuable instrument which Mendel has put into the hand of the breeder is the power of effecting the combination in one strain of desirable characters existing in separate strains, with great swiftness and precision. If the two characters we wish to combine are recessive ones, our task is an easy one, for we can effect their association in 1 individual in every 16 in the F2 generation. If, however, it is a dominant one, we have to wait till the following generation in order to determine which of the individuals bearing the dominant character are heterozygotes and which homozygotes.

[1] Royal Horticultural Society, Third International Conference on Genetics, p. 376.

But we need not multiply instances. It must be sufficiently evident that the value of the tool which has been put into the hand of the breeder of animals and plants is such as can hardly yet be estimated.

Having now given examples of some of the more salient hereditary phenomena with which the Mendelian has been able to deal, and having made a brief reference to the economical importance of by-products of Mendelian investigation, we must resume the thread of the story and see whither it leads.

The culmination of Mendelian speculation is reached in the suggestion—for it is no more than that at present—that the inheritance of sex is Mendelian; that "male" and "female" represent two allelomorphs of a pair, like yellowness and greenness in peas. Sex certainly is a character which is inherited alternatively—that is to say, in organisms in which bi-sexual reproduction is the rule, an individual exhibits either the character of one parent or that of the other, but never a mixture of the two. It is a male or a female. But there is one profound difference between the hereditary relationship of the two characters, male and female, and the two characters, yellow and green; in the latter, one character (yellow) is always dominant over the other (green), in the former this is manifestly not the case. Let us see how the matter is dealt with by Castle, who was the first to formulate definitely the theory of the Mendelian inheritance of sex in a paper entitled "The Heredity of Sex."[1] He supposes that half of the germ-cells of every male individual contain the unit character "male," and half the unit character "female"; and that the germ-cells of females are similarly constituted. Now the result of the random union of a number of such spermatozoa and ova would be: 25 per cent. ♂♂ zygotes, 50 per cent. ♀♂, and 25 per cent. ♀♀. We see at once that all the homozygotes—the ♂♂s and the ♀♀s—if they mated with their like (*i.e.* ♀♀ with ♀♀, or ♂♂ with ♂♂) would be capable of producing members *of one sex only*. This difficulty is got over by saying that there is no reason to suppose that such sexually pure—*i.e.* homozygous—individuals exist; and Prof. Castle quotes cases which tend to show that in reality every organism, whether male or female, is potentially a hermaphrodite, and

[1] *Mus. Comp. Zool. Harvard*, vol. xl. No. 4.

possesses the characters of the opposite sex to that to which it belongs in a latent state. It is well known that the removal of the generative organs of an animal often results in the appearance of the secondary sexual characters of the opposite sex; for example, the human eunuch has the high voice and the distribution of fatty tissue which is characteristic of the female. The most decisive case is perhaps that which is cited by Darwin, who relates that when the domestic cock is crossed with the hen pheasant, those of the offspring which happen to be males *have the secondary sexual characters of the male pheasant.* There is abundant evidence over and above that cited by Prof. Castle for the truth of his contention that members of both sexes are potentially hermaphrodite. So high an authority as Dr. Curt Herbst concludes, after an exhaustive scrutiny of a great mass of evidence, first, that the presence in a functional state of the generative organs of a particular sex are an indispensable condition for the elaboration of the secondary sexual characters of that sex; and, secondly, that the functional generative organ exercises a negative influence—*preventing the appearance of the secondary sexual characters of the opposite sex.*[1]

To return therefore to our argument, Prof. Castle contends—and we have seen that his contention is supported by independent evidence—that the individuals of a normally bi-sexual species are not sexually pure, but potentially hermaphrodite. From this he concludes that the homozygous individuals ♀♀ and ♂♂ do not exist. He accounts for their non-existence by supposing that the unions between ova and spermatozoa bearing similar sexes are infertile. And he adduces evidence, other than the *a priori* considerations we have spoken of, for this view. Only half the unions are fertile, namely, those between ova and spermatozoa bearing dissimilar sexes. And, in this way, only heterozygotes are produced which are capable of producing both sexes. Furthermore, to account for the fact that half of these heterozygotes display the male and half the female primary and sexual characters, we have to suppose that in the case of the allelomorphic pair "male" and "female," we have alternative dominance of either of the pair, as opposed to the fixed dominance of one of the pair which obtains in the ordinary Mendelian pairs.

We have stated that it has been shown that the characters

[1] *Formative Reize*, p. 76.

of one sex are latent in the opposite one. It is extremely important that this phrase "latent" should not be misconstrued. The manner in which the Mendelians picture this "latency" is to suppose that the members of both sexes are heterozygotes, half of whose germ-cells contain the male character and half the female character. They do *not* believe—and this is the essence of the Mendelian doctrine of gametic purity—that the germ-cell which produces a female contains maleness as well. Maleness would only be admitted to be latent in a woman in the sense that greenness is latent in a cross between a green and a yellow pea.

There is another sense in which the phrase *latent* is used which must not be misconstrued. When a grey-skinned was crossed with a white-skinned pea, the hybrids, which were grey with purple spots, gave in F_2 nine greys with purple spots, three greys, and four whites, three of which, it will be remembered, were whites carrying purple spots, which was not manifested because the grey was absent. Bateson protests against the statement that purple spot is latent in these whites. "Sulphate of copper," he says, "is blue and chloride of copper is green, but it would be improper to speak of blue as latent in sulphuric acid, or of green as latent in hydrochloric acid."

STEREO-CHEMISTRY AND ITS APPLICATION TO PHYSIOLOGY

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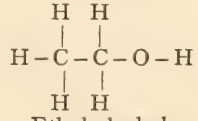
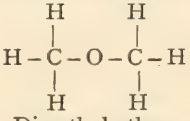
When two substances contain equal numbers of similar atoms and yet show a difference in properties, they are said to be *isomeric*. In the great majority of cases isomerism is due to a structural difference between the compounds in question—*i.e.* though they are made up of the same atoms, these atoms are differently linked together in the several substances. For example, ethyl alcohol and dimethyl ether are isomeric substances, both having the formula C_2H_6O; in the alcohol the oxygen atom links together a carbon and a hydrogen atom, while in the other case it unites two carbon atoms:



Ethyl alcohol.



Dimethyl ether.

This view sufficed for a time to explain nearly every case of isomerism known; but as more and more facts were accumulated, it became evident that some examples of isomerism could not be classed under this head; for compounds were discovered whose structures were identical, while very considerable differences were found in their properties. Organic chemists were thus forced to seek some new explanation for these phenomena.

It had been observed that several of these isomeric bodies had a peculiar influence on polarised light. It is well known that many crystalline compounds in the solid state will rotate the plane of polarisation of a polarised ray passed through the crystal; but since quartz possesses this property only when crystalline and not when in a state of amorphous silica, it is evident that we are dealing in its case merely with the influence of crystalline structure. But if we take a crystal of natural tartaric acid and dissolve it in water, so that it loses its crystalline form, we find that in solution it still has an action on the plane of polarisation. Similarly, camphor when fused does not

lose its power of rotating the plane of polarisation, though it has lost its crystalline character. In the case of these substances, therefore, the influence exerted on the plane of polarisation is not due to the same cause as the rotatory power of the quartz crystal; it is rather to be sought within the molecule itself.

It has been found that these *optically active* substances exist in two forms, one of which rotates the plane of polarisation to the right, while the other isomer rotates it through an equal angle to the left. This has led to the adoption of the current nomenclature, wherein the name of the right-rotating substance has the prefix *dextro* attached to it, while the left-rotating variety is termed the *lævo* isomer. Thus we speak of dextro camphor and lævo camphor, or simply *d*-camphor and *l*-camphor. Now, obviously, if we mix equal quantities of the dextro and lævo isomer together, the resulting mixture will have no influence upon the plane of polarisation; for the action of the right-rotating substance will be counteracted by the equal and opposite effect of the left-rotating body, and the mixture will be inactive by *external compensation*. Under certain conditions it is found that the dextro and lævo molecules combine together to form an actual inactive compound, which is termed a *racemic* substance (usually abbreviated to *r* or *dl*). The dextro and lævo bodies are usually referred to as *optical antipodes*.

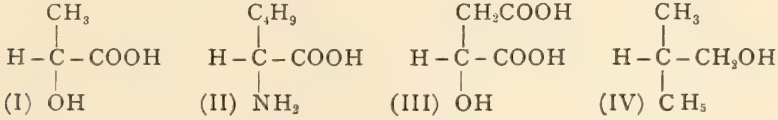
The first successful step in the study of these substances was made by Pasteur[1] in 1860, when he took up the question of the tartaric acids. He was able to show how to isolate the dextro and lævo forms from the racemic compound, discovering no fewer than three separate methods of attaining this object. He showed, further, that while racemic tartaric acid crystallizes in holohedral form, the dextro and lævo isomers show hemihedrism, the dextro crystal being the mirror image of the lævo crystal. A consideration of the general properties of the three substances led Pasteur to the conclusion that in the dextro and lævo forms the atoms might be grouped in spirals or situated at the corners of a tetrahedron. He was unable, in the elementary state of structural chemistry at that time, to do more than put this forward as a conjecture, and it remained for two later investigators to reap the credit of establishing the correctness of this view.

[1] Pasteur, *Recherches sur la dissymmétrie moléculaire des produits organiques naturels*, Paris (1860).

Pasteur believed that the optical activity of the tartaric acids was undoubtedly due to an asymmetric arrangement of which the right-handed form was the mirror image of the left-handed variety, just as a left-handed glove is a mirror image of a right-handed one. Thirteen years later, in 1873, Wislicenus[1] proved that active and inactive lactic acids had identical structures; and in his examination of the question, added, "The facts force us to explain the difference between isomeric molecules of similar structure by a different arrangement of atoms in space."

These suggestions did not lie dormant for any length of time, for in 1874 Le Bel[2] and van't Hoff[3] simultaneously and independently published papers in which the foundations of modern stereo-chemistry were laid.

Le Bel and van't Hoff pointed out that in every case where optical activity had been observed in a compound, the substance in question contained at least one *asymmetric carbon atom*, *i.e.* an atom whose four valencies are attached to four different radicles. Examples of this are found in lactic acid (i), leucine (ii), malic acid (iii), and amyl alcohol (iv), represented in the formulæ below, in each of which the asymmetric atom lies in the centre of the figure:



In the literature of that time, some cases were recorded which conflicted with this view, but later work has proved them to be due to faulty observation, and the Le Bel-van't Hoff theory has been completely established.

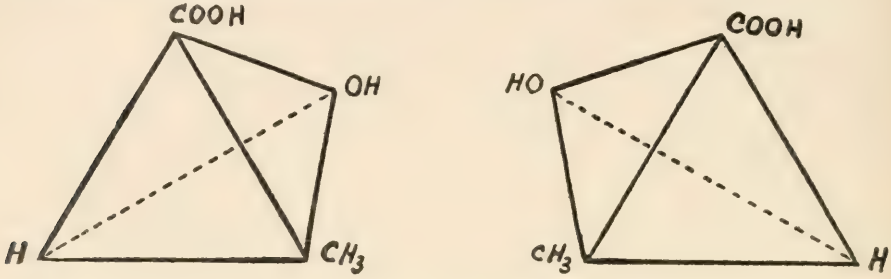
Now, when we examine the problem in the light of this evidence, we find that it is at once simplified. We need only recur to Pasteur's view that atoms in optically active compounds are situated at the corners of a tetrahedron, and the matter becomes clear. Let us suppose that the asymmetric carbon atom is situated at the centre of a tetrahedon, and that the four groups attached to it lie at the tetrahedron's corners. In the

[1] Wislicenus, *Annalen der Chem.*, **167**, 343 (1873).

[2] Le Bel, *Bull. Soc. chim.*, [2], **22**, 377 (1874).

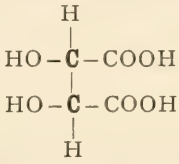
[3] van't Hoff, *Voorstell tot uitbreidung der structuur-formules in de ruimte*, Utrecht (1874).

case of lactic acid, we shall find that two arrangements are possible, each being the mirror image of the other:

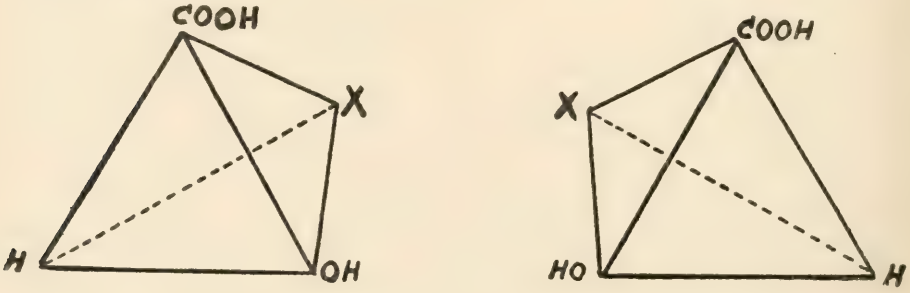


The two arrangements are unsuperposable, being related to one another as a man's right hand is to his left. Compounds which owe their difference to an arrangement of atoms in space are said to be *stereo-isomeric.*

We must now consider the effect of introducing a second asymmetric carbon atom into the molecule. This was first observed by Pasteur in the researches on the tartaric acids which we have already mentioned. When we examine the structural formula of tartaric acid, we see that it contains two asymmetric carbon atoms, which are marked by heavy type:



If we divide the molecule into two halves of identical structure, —CH(OH)COOH, we shall see that we have now three possible arrangements of atoms in space instead of two, as in the case of lactic acid. Instead of the second group —CH(OH)COOH, let us write X for convenience; then, as before, we have the two arrangements:



These represent the right-handed and left-handed varieties of the grouping XCH(OH)COOH. But now we have still to consider the grouping of the atoms in X, the second radicle $-CH(OH)COOH$. They also may be arranged in dextro or lævo form. Now, if we call the rotatory power of the one half of the molecule A, we shall find that first we have

$$+A \qquad\qquad -A$$

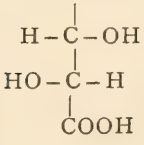
and to each of these we can add a dextro or a lævo form of the second half molecule, which has also a rotatory power, A. This gives us :

$+A$	$+A$	$-A$	$-A$
$+A$	$-A$	$+A$	$-A$
(1)	(2)	(3)	(4)

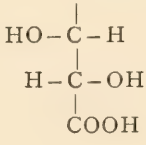
Form (1) and form (4) represent dextro- and lævo-rotatory bodies having a rotatory power of twice A. But when we examine forms (2) and (3) we find that they have no rotatory power at all, one half of the molecule counteracting the other half, just as one molecule of dextro camphor counteracts a molecule of lævo camphor and produces inactive camphor. The inactivity of the tartaric acid, however, depends upon compensation *within* the molecule itself, and the case is said to be one of *internal compensation.* Internally compensated tartaric acid is usually termed meso-tartaric for the sake of convenience.

The tetrahedron symbol does not lend itself to easy reproduction in printing, so other means were devised to represent the *configuration* or space arrangement of atoms in a compound. The method suggested by Fischer is the most generally employed. To use his formulæ, the tetrahedron model is first supposed to be built up in the usual way ; and then, after laying it on a sheet of paper, the positions of the groups of atoms are projected upon the paper. As an example, we may draw the formulæ of the tartaric acids, giving a sketch of the tetrahedra in each case :

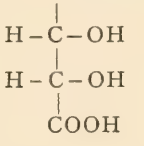
1. **d**-tartaric.

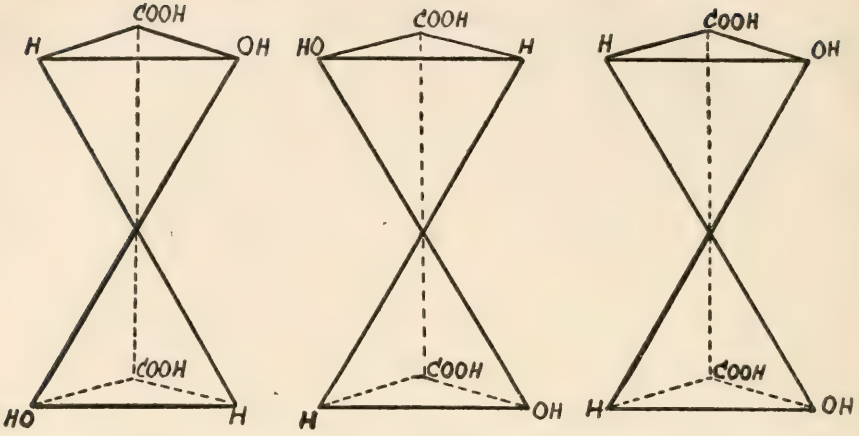


2. **l**-tartaric.



3. Meso-tartaric.





An equimolecular mixture of (1) and (2) gives racemic acid.

One point must be noticed. It might be supposed that if the two tetrahedra in the tartaric acids were to revolve around their common axis, the one isomer could be changed into the other, but this is not the case. The configuration of each isomer depends upon the *order* in which the groups are disposed around the tetrahedron, and no revolution can alter this. It is assumed that in these isomers the two tetrahedra can vibrate quite freely ; but it is probable that, under any given conditions, they will come into equilibrium in some fixed position.

In order to make clear the difference in physical properties which is produced by differences in the arrangements of atoms in space, a table is given below which includes the chief properties of the dextro, lævo, meso, and racemic forms of tartaric acid :

	Dextro	Lævo	Meso	Racemic
Melting-point . . .	170°	170°	140°	206°
Affinity Constant . .	0·097	0·097	0·060	0·097 [1]
Specific Gravity . .	1·755	1·754	1·666	1·697
Solubility in 100 parts of water at 15° .	136	136	125	17

We must now consider what influence is exerted upon certain reactions by these differences in the spacial arrangements of atoms ; and, in the first instance, we may deal with the actions of certain organisms upon racemic compounds. It has been observed by many observers,[2] of whom Pasteur was the pioneer,

[1] This is probably not the true value for K, as in dilute solutions the racemic acid dissociates into the two antipodes.

[2] A complete set of references is to be found in Landolt's *Optische Drehungsvermögen organischer Substanzen*, Brunswick ; or in Winther, *Ber.*, **28**, 3022 (1895).

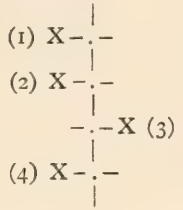
that when moulds of various kinds were allowed to grow in a racemic solution to which phosphates or other nutrient matter had been added, the solution gradually became optically active, an excess of one antipode being left. At one time it was supposed that the mould was unable to attack one antipode, and confined its destructive action entirely to the other; but the work of Frankland and MacGregor,[1] and of McKenzie and Harden,[2] showed this to be erroneous; the mould destroys both antipodes, but appears able to attack one much more rapidly than the other. This difference in action must be due to the difference in configuration between the two antipodes. Since some moulds attack the dextro form while others destroy the lævo variety, it is possible to obtain either the left-handed or the right-handed form of a given body by utilising the appropriate mould. For instance, if we treat racemic mandelic acid with the ferment *Penicillium glaucum*, an excess of dextro mandelic acid results, while lævo mandelic is obtained by using *Saccharomyces ellipsoideus*. Fischer and Thierfelder[3] have noted another case of fermentation in which even a slight difference in the configuration appears to exert a considerable influence. They treated the dextro forms of glucose, mannose, galactose, and talose with the same ferment, and found that while the first two were easily fermented, galactose was attacked only with difficulty, while talose was not affected. When we examine the space formulæ of the four bodies, a possible explanation of this difference suggests itself:

Glucose	Mannose	Galactose	Talose
CH_2OH	CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	HO.H	HO.H
HO.H	HO.H	H.OH	H.OH
H.OH	H.OH	H.OH	H.OH
HO.H	H.OH	HO.H	H.OH
CHO	CHO	CHO	CHO
Ferment easily.		Fermentable	Unfermented.

Fischer supposes that ferment and sugar fit each other as a key fits a lock; so that certain "wards" of the sugar can be reached only if the ferment has a configuration similar to that of the sugar. If we symbolise part of the ferment in the same way as the sugars, and represent by X the "ward" which

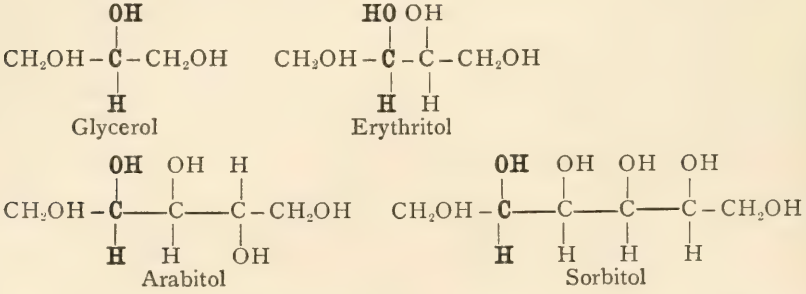
[1] Frankland and MacGregor, *Journ. Chem. Soc.*, **63**, 1034 (1893).
[2] McKenzie and Harden, *Journ. Chem. Soc.*, **83**, 424 (1903).
[3] Fischer and Thierfelder, *Ber.*, **27**, 2035 (1894).

touches the hydroxyl group, we shall find that a perfect ferment for glucose would be written thus:

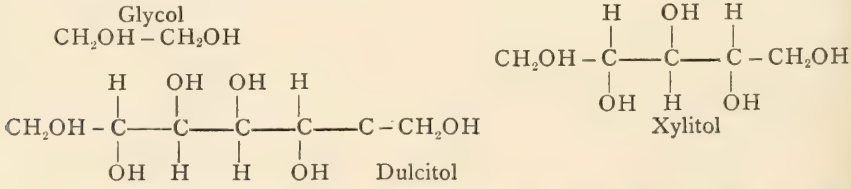


Here four "wards" come into play. In the case of mannose, only three of these (1, 2, and 3) are able to act; in galactose, 1, 3, and 4 would be able to attack the hydroxyl groups; while in talose only two (1 and 3) could come into action. This analogy of lock and key must not be pushed too far, but there certainly appears to be some relation between configuration and the ease of fermentation in certain compounds.

Results of a somewhat similar nature were obtained by Bertrand[1] in his studies of the action of the sorbose bacterium (*Bacterium xylinum*) on certain polyhydric alcohols. He found that the following alcohols were attacked by the organism:

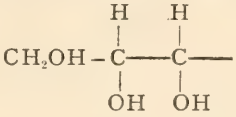


In each case the heavily printed —CHOH— group is oxidised to —CO—. On the other hand, compounds such as those below are not attacked in this way:



[1] Bertrand, *Bull. Soc. chim.*, [3], **19**, 347, 947, 999 (1898); *Compt. rend.*, **122**, 900 (1896); **126**, 762 (1898).

An examination of the formulæ shows that two conditions must be fulfilled before the bacterium can act. In the first place, the compound must contain a $-CHOH-$ group next a $-CH_2OH$ radicle; and in the second place it must have a space formula in which two hydroxyl groups lie next each other. In other words, unless a compound contains the grouping



the bacterium cannot attack it.

The foregoing results are sufficient to show that an intimate relationship exists between the molecular configuration of substances and the readiness with which they are attacked by ferments. Since this relationship exists in these cases, it is natural to expect a similar connection between the configuration of a substance and its behaviour in the bodies of animals. A large portion of all animal tissue is made up of asymmetric substances, and it appears probable that if an optically active substance is digested, either the dextro or the lævo form will react more easily than its antipode during the process.

When we consider the case of the three possible substances (dextro, lævo, and racemic), and suppose for the sake of convenience that the dextro compound is more easily assimilated than the lævo antipode by a given animal, we shall find that the racemic substance offers a further peculiarity; for if it passes through the organism as an actual compound, both its components will be destroyed to a certain equal extent, while if it breaks down into a mixture of its constituents, the dextro form will be attacked while the lævo isomer is unassimilated. We shall meet several cases of this kind in the work about to be described.

The simplest case of all is that of the tartaric acids, which has been described by Brion.[1] He found that racemic acid was least oxidised in the animal organism; next came dextro tartaric; while lævo tartaric and meso tartaric were most strongly acted upon. This proves that racemic acid, in its passage through the organism, is not decomposed into a mixture of dextro and lævo forms; as in that case the lævo form would be destroyed and a preponderance of the dextro form would remain.

[1] Brion, *Zeit. physiol. Chem.*, **25**, 283 (1898).

Further, the action of the animal tissue upon meso tartaric acid can be explained in the following way. Lævo tartaric acid is made up of two radicles, $-CH(OH)COOH$, each of which is arranged in lævo configuration, which is favourable to the attack of the organism; dextro tartaric acid, being composed of two dextro radicles, $-CH(OH)COOH$, offers no foothold to the destructive action of the tissues: the meso form, being made up of one dextro and one lævo radicle, offers a point of attack in the latter, and is therefore destroyed.

Neuberg and his collaborators have studied that part of the subject, and have examined several cases of the behaviour of optical antipodes in the animal body. We may take the case of the three arabinoses and their derivatives[1] as an example. The arabinoses are sugars which have the structural formula $CH_2OH . CH(OH) . CH(OH) . CH(OH) . CHO$. The figures below represent in each case the percentage of substance recovered from the urine of rabbits; column I shows the results obtained when the substance was introduced through the mouth, II when introduced subcutaneously, and III intravenously:

	I	II	III
Lævo arabinose	14·5	7·1	28·3
Racemic arabinose . . .	28·5	31·7	29·0
Dextro arabinose . . .	31·2	36·0	31·0

These results agree fairly well among themselves, when allowance is made for inevitable experimental differences. The three sodium salts of the arabonic acids, $CH_2OH . CHOH . CHOH . CHOH . COONa$, show similar differences, though less of the lævo than of the dextro isomer is attacked in their case. When the corresponding alcohol arabite, $CH_2OH . CHOH . CHOH . CHOH . CH_2OH$, was supplied to the animal, small quantities of pentoses, $CH_2OH . CHOH . CHOH . CHOH . CHO$, appeared in the urine, one of the $-CH_2OH$ groups at the end of the chain being oxidised to $-CHO$.

A very important result was obtained by Neuberg and Wohlgemuth[2] in the case of the human subject. In certain diseases it is found that *racemic* arabinose makes its appearance. Now, when racemic arabinose was supplied to a human subject it was found that a considerable action took place, about two-

[1] Neuberg and Wohlgemuth, *Ber.*, **34**, 1745 (1901); *Zeit. physiol. Chem.*, **35**, 41 (1902).

[2] *Ibid.*

thirds of the excreted substance being in the active form, showing that the racemic compound had been broken down into its components, one of which had been destroyed. It is therefore obvious that the formation of racemic arabinose due to disease must take place in an organ so situated that after being liberated from it the arabinose is not submitted to any process of decomposition.

Since a difference in configuration such as exists between dextro and lævo forms has such a pronounced effect on the nutritive values of the arabinoses, it is not astonishing that Nagano[1] found a similar difference between lævo xylose and lævo arabinose, the former being more easily absorbed by the system. The configuration formulæ of the two substances are shown below.

l-Xylose	l-Arabinose
CH_2OH	CH_2OH
HO.H	H.OH
H.OH	H.OH
HO.H	HO.H
CHO	CHO

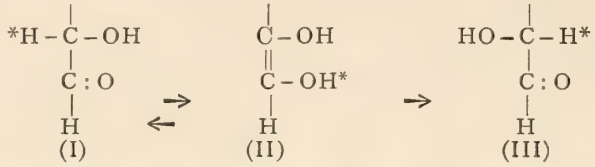
Analogous results were obtained by Neuberg and Meyer[2] in the case of the mannoses, $CH_2OH.CHOH.CHOH.CHOH.CHOH.CHO$. The dextro form appeared best suited for nutrition. The chief point of interest for stereochemical workers lies in the fact that during the passage of the dextro, lævo and racemic compounds through the system derivatives of another sugar, glucose, were produced. The formulæ of *d*-mannose and *d*-glucose are given below.

d-Mannose	d-Glucose
CH_2OH	CH_2OH
HO.H	HO.H
HO.H	HO.H
H.OH	H.OH
H.OH	HO.H
CHO	CHO

As can be seen from an inspection of the formulæ, the change from mannose to glucose necessitates the rearrangement of the groups attached to the lowest carbon atom in the formula. Such a rearrangement implies no great strain on the molecular

[1] Nagano, *Pfluger's Archiv.*, **90**, 389 (1902).
[2] Neuberg and Meyer, *Zeit. physiol. Chem.*, **37**, 530 (1903).

arrangement, however, as it may be supposed to take place by a wandering of a hydrogen atom, thus:



The form (II) is unstable. If a model be built up to represent these formulæ, it will be found that when the hydrogen atom marked with an asterisk wanders back from the position (II) it may give rise to (I) or (III). The action of the living tissues in this case is evidently exerted to bring about the change of (II) into (III) rather than of (II) into (I).

Rosenfeld[1] has found that sugars are excreted in urine in the following order: galactose, mannose, glucose; while the alcohols follow the analogous order: dulcite, mannite, sorbite.

CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	HO.H
H.OH	HO.H	HO.H
H.OH	H.OH	H.OH
HO.H	H.OH	HO.H
CHO	CHO	CHO
d-Galactose	**d**-Mannose	**d**-Glucose

CH_2OH	CH_2OH	CH_2OH
HO.H	HO.H	HO.H
H.OH	HO.H	HO.H
H.OH	H.OH	H.OH
HO.H	H.OH	HO.H
CHOH	CH_2OH	CH_2OH
Dulcite	**d**-Mannite	**d**-Sorbite

These differences are probably caused by some reaction similar to that which takes place in the selective fermentation of certain sugars, which was described above.

Having dealt with the influence of the configuration of optical antipodes upon their nutritive value, we must turn to another side of the question, and consider the relations between the configurations and toxic qualities of various compounds. No general rule can be laid down in this case; for, as in the case of nutrition, the experimental data are here far too meagre to allow of generalisation.

In the first place, it is advisable to point out that in some cases influences intervene which are only indirectly

[1] Rosenfeld, *Centralblatt f. innere Medicin*, **21**, 177 (1900).

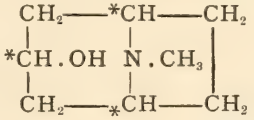
attributable to the special arrangement of atoms in space. For example, Chabrié's [1] experiments on the toxicity of the tartaric acids are stated by Cushny [2] to be unreliable, as the toxic agent in this case is really the hydrogen ion and not the acid itself. Since the configuration of the acid's molecule influences its ionization, however, it should in this way have some effect upon its toxicity also. Chabrié's figures are given below. They are calculated in the following way: Let x be the weight of acid required to kill one kilogram weight of an animal in one minute, p the weight of acid, and w the weight of animal used, and T the time required to kill determined by experiment, then

$$\frac{1}{x} = \frac{1000\,p.\,T}{w}$$

	$\frac{1}{x}$
Lævo-tartaric acid	34·26
Dextro „ „	104·24
Racemic acid	165·25
Meso-tartaric acid	196·27

It will be seen from a comparison of these figures with Brion's results, which have already been given, that there is no close connection between the two.

Owing to their applications in medicine, the behaviour of compounds of the tropine series has been investigated with more thoroughness than that of other isomers. The parent substance, tropine, has the following structure:



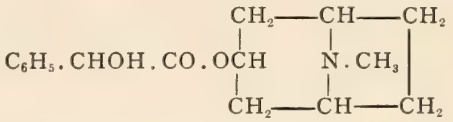
in which three carbon atoms (marked with asterisks) are asymmetric. When tropine (melting-point 62°) is treated with sodium amylate, it is converted into an isomeric body, pseudo-tropine (melting-point 108°). The two compounds have exactly the same structure, and the difference between them is due, probably, to the different arrangement of the —CH.OH— radicle. Ladenburg [3] has suggested another explanation depending

[1] Chabrié, *Compt. rend.*, **116**, 1410 (1893).

[2] Cushny, *Journ. Physiol.*, **30**, 193 (1904).

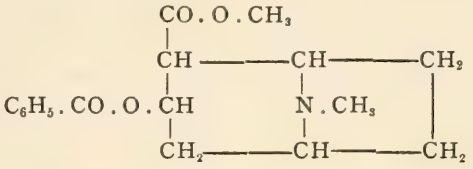
[3] See Ladenburg, *Ber.*, **26**, 854 (1893); **36**, 3694 (1903); and Groschuff, *ibid.* **34**, 2974 (1904), for examples of this type of isomerism.

upon the special arrangement of groups around the nitrogen atom. Whichever be true, the isomerism of tropine and pseudo-tropine is caused by spacial, not structural differences. When we allow mandelic acid to react with the hydroxyl groups of tropine and pseudo-tropine, we obtain two stereoisomeric esters, each of which has the following structure:



The ester obtained from tropine has a strong mydriatic action, while the pseudo-tropine ester has no such property.

When one of the hydrogen atoms of tropine is replaced by a carboxyl group, tropine carboxylic acid is formed; and when the alcoholic radicle of this substance is benzoylated while the carboxyl group is esterified with methyl alcohol, we obtain cocaine, which has the formula:



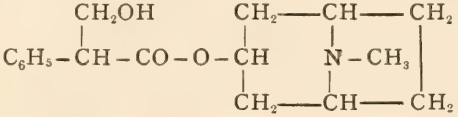
Cocaine, of course, since it contains asymmetric carbon atoms, exists in two antipodic forms of equal and opposite rotatory power. Poulsson[1] found that when applied to the tongue the paralysing action of dextro cocaine was stronger and set in more rapidly than that of lævo cocaine; but, on the other hand, the effect of the dextro isomer was not so permanent as that of the lævo antipode. In the case of rabbits and frogs, the fatal dose seems to be the same for each isomer. Ehrlich and Einhorn[2] arrived at similar results.

According to Hesse[3] the therapeutic action of scopolamine and the corresponding racemic compound atroscine differ from each other.

Cushny[4] investigated the actions of lævo hyoscyamine and

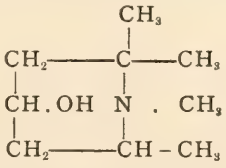
[1] Poulsson, *Archiv exp. Path. u. Pharmak.*, **27**, 309 (1890).
[2] Ehrlich and Einhorn, *Ber.*, **27**, 1870 (1894).
[3] Hesse, *Journ. f. prakt. Chem.*, [2], **64**, 353 (1901).
[4] Cushny, *Journ. Physiol.*, **30**, 193 (1904).

atropine, which is the corresponding racemic form. These substances are the tropine esters of tropic acid, and have the formula :



It was found that both atropine and *l*-hyoscyamine have the same action upon the central nervous system of animals, the effects being not only qualitatively but also quantitively identical. When applied to the spinal cord reflexes, atropine has a more powerful influence than the active isomer; but this is reversed in the case of the nerve ends of the heart, the salivary glands, or the pupil of the eye; for at each of these points *l*-hyoscyamine has an effect twice as strong as that produced by atropine. From these results we can deduce the probable effect of dextro hyoscyamine. We know that *dl*-hyoscyamine (atropine) has the same effect as *l*-hyoscyamine on the central nerve system of mammals; therefore in this case dextro and lævo forms must have the same effect. But, on the other hand, *dl*-hyoscyamine has a greater effect than *l*-hyoscyamine on the spinal cord, so that here, obviously, *d*-hyoscyamine must exert a greater influence than *l*-hyoscyamine. In the case of the heart, the effects are again reversed; for since here *l*-hyoscyamine is twice as powerful as *dl*-hyoscyamine, it appears that *d*-hyoscyamine must be almost without action. Of course this reasoning assumes that the racemic compound breaks up into the two antipodes before it acts upon the various nerves.

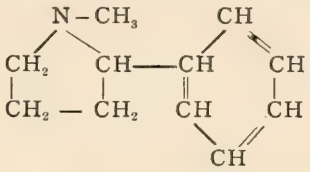
Two other substances should now be described, as they are closely allied to the tropine group. If in the formula of tropine we replace the radicle $-CH_2-CH_2-$ by two methyl groups, and at the same time exchange a hydrogen atom of a $-CH-$ group for a methyl radicle, we obtain the following formula, which represents N-methyl-vinyl-diacetone-alkamine :



Like tropine itself, this compound exists in two isomeric forms, the mandelic ester of one being an oil, while that of the other

melts at 113°. In this case also the labile isomer has a mydriatic action, while the stable isomer lacks that property.

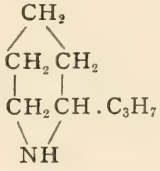
The actions of the two antipodic forms of nicotine:



have been studied by Mayor,[1] who found that the lævo form was twice as poisonous as the other. When dextro nicotine is injected no pain is felt; but when the lævo isomer is used it produces both pain and excitation. The lævo antipode causes paralysis, spasms, retardation of the action of the heart, and finally death by the cessation of respiration; while the same dose of dextro nicotine produces only a strong shivering fit, which soon passes off.

Only one or two other cases need be mentioned in this division of the subject. Albertoni[2] has shown that the dextro-rotatory compound cinchonine differs in action from its lævo-rotatory isomer cinchonidine. The latter has a slower action, requires a larger dose to produce the same effect as the dextro isomer, gives rise to vomiting, and has a marked tendency to cause spasms. Quinine and quinidine, which are also optical isomers, differ in physiological action as well, quinidine having no narcotic properties, though showing the febrifugial action of quinine.

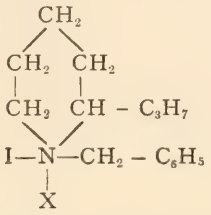
Coniine has the structure:



and as it contains an asymmetric carbon atom it occurs in active and racemic forms. Ladenburg and Falk[3] compared the action of the dextro antipode with that of the racemic form, but were unable to detect any difference between the two effects.

[1] Mayor, *Ber.*, **38**, 597 (1905).
[2] Albertoni, *Archiv exp. Path. u. Pharmak.*, **15**, 272.
[3] Ladenburg and Falk, *Annalen d. Chem.*, **247**, 83 (1888).

Hildebrandt,[1] examining ethyl, propyl, butyl, and iso-amyl derivatives of benzyl-coninium iodide, found that the isomer with the lower melting-point had also the weaker physiological action. The general formula of these bodies is shown below, the position occupied by the ethyl, propyl, butyl or iso-amyl radicle being indicated by X.

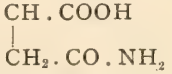


In the preceding paragraphs we have shown that the influence of the antipodic arrangement of atoms in a molecule is well marked in many cases. We must now mention several instances which show that differences in the configuration of compounds may affect our senses.

In the first place, we may point out that the crystals of the dextro and lævo forms of sodium ammonium tartrate differ from each other and from those of sodium ammonium racemate. The optically active compounds crystallise in hemihedral form, and the crystal of the *d*-salt is the mirror-image of that of the *l*-salt. The racemic salt exhibits no hemihedral faces in its crystals. The spacial arrangement of atoms, since it lies at the root of this difference in crystalline form, certainly affects our sense of touch.

Passing now to the question of smell, it has been found by Werner and Conrad[2] that the methyl esters of the two optically active trans-hexahydroterephthalic esters have different odours; while Schmidt and Tiemann observed that racemic terpenes were less odoriferous than the corresponding active isomers.

Taste, in its turn, is affected in the same way, for Piutti[3] states that the dextro and lævo forms of asparagine



[1] Hildebrandt, *Ber.*, **38**, 597 (1905).
[2] Werner and Conrad, *Ber.*, **32**, 3052 (1899).
[3] Piutti, *Compt. rend.*, **103**, 134 (1886).

have different tastes, that of the *d*-form being sweet, while the *l*-isomer is insipid. Fischer and Hagenbach[1] state that lævo leucine has a weakly bitter taste, while the dextro form is quite sweet. A similar difference was noted by Menozzi and Appiani,[2] who found that *d*-glutaminic acid was sweet, while the lævo form was tasteless. Glutaminic acid has the formula:

$$\begin{array}{l} NH_2 . CH . COOH \\ \quad\quad | \\ \quad CH_2 . CH_2 . COOH. \end{array}$$

In the case of mannose and glucose, the evidence is conflicting; for van Ekenstein[3] states that mannose is sweet, while glucose is bitter; but this is contradicted by Neuberg and Mayer.[4] Sternberg[5] considers that as a rule the difference between the isomers is quantitative rather than qualitative. If this be correct, it opens up a field for speculation. Marckwald and McKenzie[6] have shown that when an active acid is esterified with a racemic alcohol, or *vice versâ*, the reaction proceeds faster with one component of the racemic body than with the other. For instance, they found that lævo menthol combines more rapidly with dextro-mandelic acid than with lævo-mandelic acid. If we recall that Pasteur conceived nerves as asymmetric organisms, the "quantitative difference" between the actions of optical antipodes upon them might be explained by supposing that the asymmetric nerve substance combines more readily with one antipode than with the other. This, however, is pure theory.

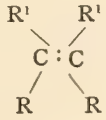
The sense of sight is the last one with which we can deal. Byk[7] has shown that a solution of potassium copper racemate differs in tint from a solution of the potassium copper salt of dextro tartaric acid. Thus, the only sense which is not yet proved to be affected by optical isomerism is that of hearing. Even this might conceivably be influenced by differences in the rate of transmission of sound in active and racemic substances; but, so far, no experiments have been made in this direction.

We must now turn to another branch of the subject, and

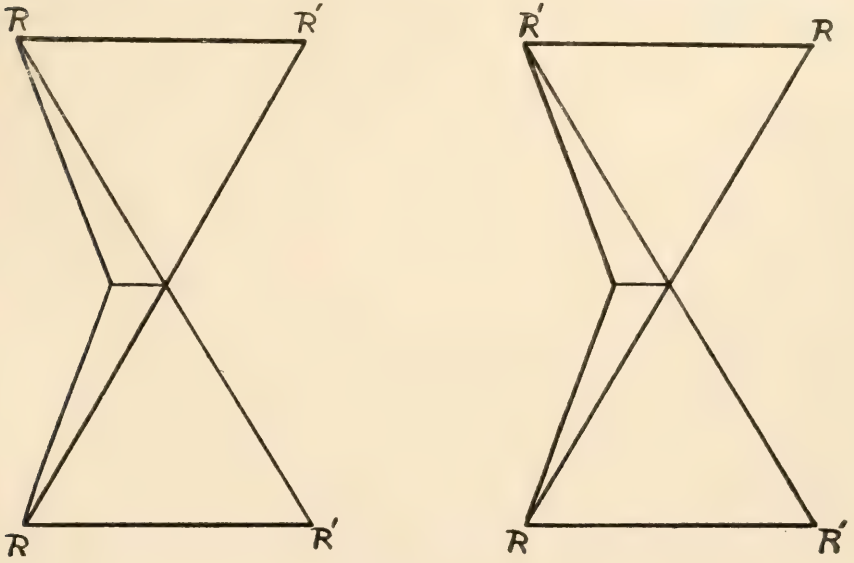
[1] Fischer and Hagenbach, *Ber.*, **34**, 3764 (1901).
[2] Menozzi and Appiani, *Atti R. Accad. Lincei* [5], **2**, II. 421 (1893).
[3] van Ekenstein, *Rec. trav. chim.*, **15**, 222 (1896).
[4] Neuberg and Mayer, *Zeit. physiol. Chem.*, **37**, 545 (1903).
[5] Sternberg, *Archiv Anat. u. Phys.*, **1898**, 457.
[6] Marckwald and McKenzie, *Ber.*, **32**, 2130 (1899).
[7] Byk, *Zeit. physikal. Chem.*, **59**, 682 (1904).

consider those cases in which isomerism is due to the presence in the molecule of a double bond between two atoms. The Le Bel-van't Hoff hypothesis assumed that, in the case of a single bond between two carbon atoms, free rotation of the atoms about their common axis was possible; but when we come to a compound containing a double bond, this postulate is abandoned, and it is assumed instead that the double linking of the atoms introduces an element of rigidity into the molecule. We may retain the tetrahedral symbols in this case also, and represent the compound ethylene, $CH_2{:}CH_2$, by two tetrahedra laid edge to edge instead of apex to apex, as in the previous cases.

When we substitute other atoms or radicles for the four hydrogen atoms, we shall find that under certain conditions we have a system which is capable of two space arrangements. The necessary conditions are simple: we need only ensure that the two groups attached to each carbon atom differ from one another. In other words, isomerism is to be expected in its simplest form in the case of an ethylene derivative.

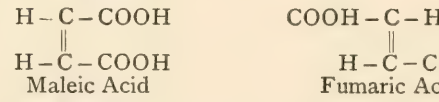


The two possible special arrangements are those represented by:



In the first case the two groups R lie one above the other, while in the second figure R lies over R^1; and since free rotation of the carbon atoms is assumed to be precluded by the nature of the double bond, no change in configuration can take place under ordinary conditions. It should be noted that all four groups RRR^1R^1 lie in one plane, so that no isomerism due to enantiomorphous arrangements of atoms is to be expected, nor have these isomers any action upon the plane of polarisation. To distinguish these isomers from those containing asymmetric carbon atoms it is usual to term them *geometrical* isomers, as distinct from optical isomers.

The best known case of geometrical isomerism is that of maleic and fumaric acids, which may be represented thus, if the tetrahedra be omitted:



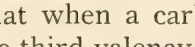
Maleic Acid — Fumaric Acid

When maleic acid is heated above its melting-point it is converted into fumaric acid. The former body is therefore termed the *labile* form, while fumaric acid is known as the *stable* isomer. As in the case of optical isomers, we may give here a table showing the principal physical properties of maleic and fumaric acids:

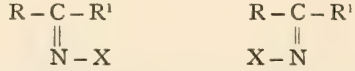
	Maleic Acid	Fumaric Acid
Melting-point	130°	Sublimes unchanged
Affinity Constant	1·17	0·093
Specific Gravity	1·590	1·625
Solubility in water	1:2	1:150

An extension of the hypothesis of geometrical isomerism to nitrogen compounds was made in 1890 by Hantzsch and Werner.[1] They assumed that when a carbon atom is doubly linked to a nitrogen atom, the third valency of the nitrogen atom is directed at a certain angle to the other two.

Now, in the compound



it is obvious that X may be supposed to lie near R or R^1; so that in this case also we have the possibility of two geometrical isomers:



[1] Hantzsch and Werner, *Ber.*, **23**, 11 (1890).

Much less attention has been given to the physiological action of stereoisomers of this type; and when we examine the literature of the subject, only a few scattered references are to be found. The cause of this apparent neglect is to be found in the fact that many of the alkaloids used in medicine occur in optically active forms, while geometrically isomeric bodies find no considerable place in pharmacology.

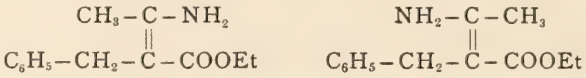
We may consider in the first place the effect which this type of isomerism exerts upon fungi. The fungus *Penicillium glaucum* grows readily in fumaric acid solution, but does not thrive in a solution of maleic acid. Using *Lupinus albus, L.*, Kahlenberg and True [1] established the following figures. When the fungus was introduced into a solution containing 116 grammes of acid in 6,400 litres of water, it died. When the solution was diluted to twice its volume, the organisms were able to live in the weakened solution. 116 grammes of maleic acid dissolved in 3,200 litres of water produced a solution incapable of supporting the organisms; but on dilution to 6,400 litres it became fit to support the fungi. These two sets of results, pointing as they do in opposite ways, seem to indicate a difference in the configurations of the active tissues of fungi, *Penicillium glaucum* being capable of attacking fumaric acid, *Lupinus albus, L.*, has a greater power of breaking down maleic acid. Further research in this field might lead to very interesting results, as the case seems to form a parallel to the action of ferments upon sugars, with which we have already dealt.

In toxic action the two acids differ considerably, as Ishizuka [2] has proved. In his experiments he took 1·94 grammes of acid for each kilogramme of dog used. This, in the case of maleic acid, proved a fatal dose; while with fumaric acid the same dose had no effect. It should be noted, however, that this result may be due to a difference in the strength of the two acids, maleic acid being much stronger than fumaric.

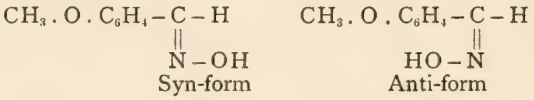
Toxic action, however, is not the only property in which these isomers show differences. It has been found that in the case of the compound benzyl-β-amidocrotonic ester, whose two configurations are shown below, the one form (M.P. 79°) is tasteless, while its isomer (M.P. 21°) has an intensely sweet

[1] Kahlenberg and True, *Botanical Gazette*, Chicago, **22**, 181 (1896).
[2] Ishizuka, *Bull. Coll. Agr.*, Tokyo, **2**, 484 (1897).

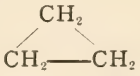
taste, which resembles that of peppermint. The two configurations are shown below:



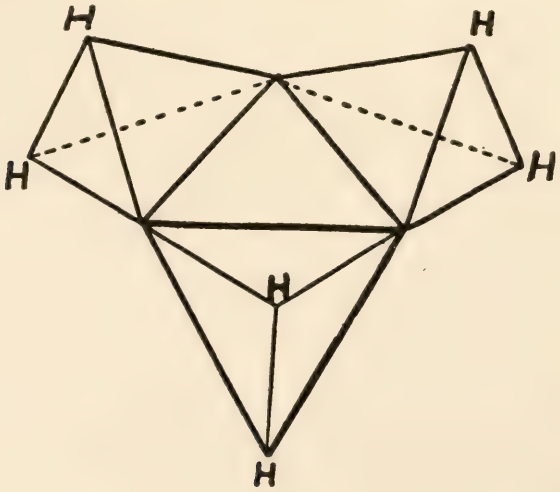
A similar example is found in the case of the aldoximes: the syn-form of anisaldoxime is tasteless, while the anti-form is very sweet:



We must next deal with another case in which the rotation of carbon atoms about their axis of junction is hindered. When three or more carbon atoms are joined together to form a cyclic compound like trimethylene:



there are two important consequences. In the first place, free rotation of the carbon atoms becomes difficult, if not impossible. This can be seen by building up a model, when it will be found that a disruption of the molecule would almost certainly result from any such rearrangement. Secondly, the six hydrogen atoms in trimethylene are arranged in two parallel planes, the carbon atoms lying in a third plane between these two and parallel to them.



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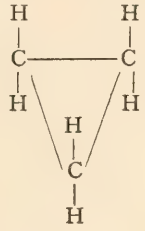
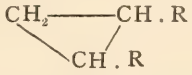
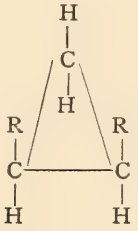


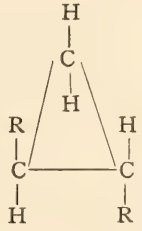
Now, here, as in the case we have already dealt with, substitution may produce a difference in configuration; for if we take the case of the compound:



we shall find that there are two possible spacial arrangements of the atoms. In the first, we have the two groups R and one hydrogen atom in the same plane, while in the second arrangement we have one R group and two hydrogen atoms in the same plane:

(I)

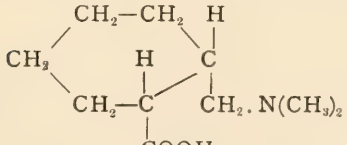




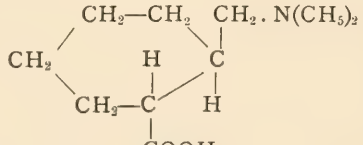
(II)

Form (I) is called the *cis*-form; form (II) the *trans*-form.

In this section two instances are known in which the two isomers differ from one another in smell. In each case the cis-form has a stupefying odour, while the trans-isomer is devoid of smell. The substances in question are the hexahydro-*o*-diethyl-benzylamine carboxylic acids:

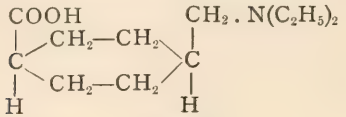


Cis-form

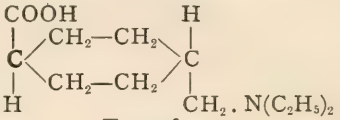


Trans-form

and the hexahydro-*p*-diethyl-benzylamine carboxylic acids :



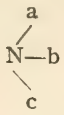
Cis-form



Trans-form

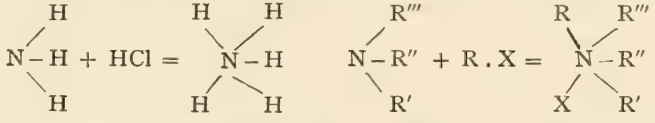
In the foregoing paragraphs we have been concerned with compounds which owed their isomerism to some peculiarity either in the arrangement of radicles round a carbon atom, or in the mode of linkage between atoms. We must now turn to the question of an isomerism which is due to other types of asymmetry, and we may commence with the case of asymmetric nitrogen.

Without going into any intricate details, it may be said that when a nitrogen atom is united to three separate radicles, no isomerism is to be found. Of course, as has been mentioned already, a nitrogen atom doubly linked to a carbon atom may give rise to isomerism, but in the case of a compound such as :



no isomerism occurs; and it is therefore assumed that the groups *a*, *b*, and *c* and the nitrogen atom lie in one plane or are free to move about in space. Were this not so, we should expect to find enantiomorphism shown by such substances.

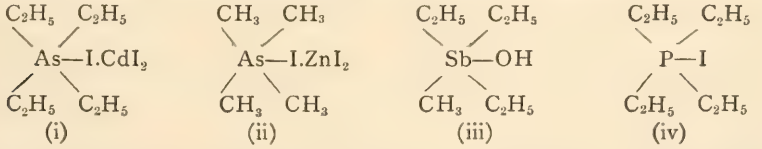
When we allow a tertiary amine to react with an alkyl halide, a quaternary ammonium salt is formed, just as ammonia and hydrochloric acid unite to form ammonium chloride :



When the four alkyl groups attached to the nitrogen atom differ from each other, as in the case of NRR′R″R‴Cl, the nitrogen atom is asymmetric, and the compound is found to exist in two enantiomorphous forms of equal and opposite rotatory power. The case is parallel to that of the asymmetric carbon atom. It is evident that in passing from the trivalent to the pentavalent condition of the nitrogen atom we have passed from a plane configuration of the molecule to one of three dimensions.

Crum Brown and Fraser[1] have shown that when certain alkaloids containing a trivalent nitrogen atom were allowed to unite with methyl iodide, they gained a new physiological property without losing any of their previous efficiency. The new attribute which they acquire by this increase in the valency of their nitrogen atoms resembles the chief property of curare, for these new methyl iodide addition products have a paralysing action upon the ends of the motor nerves of muscles. Curare itself contains a tertiary base curine, and Boehm[2] has shown that when curine is treated with methyl iodide it yields the quaternary salt curarine, which is two hundred and twenty-six times as poisonous as the mother substance, and which possesses in an acute degree the paralysing properties of curare. The most probable deduction from these results is that the change in the valency of the nitrogen atom lies at the root of these effects; but we must inquire further whether the consequent change in configuration has not some bearing upon the point.

Fortunately, the evidence on this subject is already at our disposal. We need only replace the nitrogen atom by some other atom which has the same faculty of changing from the trivalent to the pentavalent condition; and we are not hampered in our choice in this matter, as no fewer than three other elements have been examined by Vulpian.[3] The substances actually used by him were: (i) tetra-ethyl-arsonium cadmium iodide, (ii) tetra-methyl-arsonium cadmium iodide, (iii) methyl-triethyl-stibonium hydroxide, and (iv) tetra-ethyl-phosphonium iodide:



None of these substances shows the ordinary physiological behaviour of arsenic, antimony, or phosphorus, but all of them have a strong curare-like action, which seems to indicate that that action is due rather to the molecule as a whole than to the nature of the atom at the centre of the complex.

[1] Crum Brown and Fraser, *Trans. Roy. Soc. Edin.*, **25**, 707 (1868); *Proc. Roy. Soc. Edin.*, **1869**, 560.

[2] Boehm, *Archiv de Pharmacie*, **235**, 660 (1897); *Archiv exp. Path. u. Pharmak.* **6**, 101.

[3] Vulpian, *Archiv de phys. norm. et pathol.*, **1**, 472; see also Bürgi, *Archiv. exp. Path. u. Pharmak.*, **56**, 101.

Another example of the change of a plane molecular configuration into a three-dimensional one is to be found in the case of the sulphur compounds. In the alkyl sulphides having the formula R — S — R′, since there are only three groups, the configuration must be a plane one. When alkyl iodides are added to these sulphides, however, optically active substances can be produced, having the formula:

and from the occurrence of optical activity it is supposed that this case is analogous to that of the asymmetric carbon atom; and that the radicles R, R′, R″, and X are arranged at the corners of a tetrahedron whose centre is occupied by the sulphur atom. Of course this tetrahedral arrangement will persist even if the sulphur atom be not asymmetric and no optical activity is shown. Now Curci and Kunkel[1] have found that sulphine bases, such as trimethyl-sulphine hydroxide $(CH_3)_3 . S . OH$, have a pronounced curare-like action, which is lacking in the sulphides.

Similar results have been obtained by Bock[2] in his study of the ammonia derivatives of cobalt, chromium, and rhodium, which resemble each other to a certain extent. He was able to show that the nature of the metallic atom in the molecule had less influence upon the physiological action than was exerted by the general character of the compound.

Since in all these cases a change from a plane configuration to a three-dimensional one is taking place, and since, previously, we have shown how great an influence upon the physiological action of certain substances is exerted by a difference in the spacial arrangement of their atoms, we are not unjustified in assuming that the change in configuration has some influence in this case also.

Stereochemistry is usually divided into two sections. In the one division we deal with the purely static (or at least hypothetically static) relations between atoms which give rise to isomerism; in the second section we are concerned chiefly with

[1] Curci, *Archiv de pharm. et de therap.*, **4**, 1896; Kunkel, *Lehrbuch der Toxikologie* (1901).

[2] Bock, *Archiv exp. Path. u. Pharmak.*, **52**, 1, 30 (1904).

the dynamic effects of certain atomic groupings, their influence upon chemical reactions, and similar subjects. In the foregoing pages we have restricted our examination to the first division, and have dealt purely with the question of stereo-isomerism and its connection with the action of certain substances upon living tissues; but we must now turn to the second part of the subject and discuss the dynamic influence which certain atomic groups may exert upon others.

When we allow acetic acid to react with ethyl alcohol in presence of hydrochloric acid, water is eliminated and ethyl acetate is formed:

$$CH_3.COOH + C_2H_5OH = CH_3.COOC_2H_5 + H_2O$$

Now, the researches of Menschutkin, Sudborough, and Lloyd, and others[1] have shown that when substituted acetic acids are used instead of the parent substance, the amount of ester formed under given conditions decreases. The amount of this decrease depends on the complexity of the acid, and is quite independent of its strength, as the following table shows:

Formula of Acid.	Amount of Ester.	Affinity Constant.
$CH_3.COOH$	3·661	0·00180
$CH_3.CH_2.COOH$	3·044	0·00134
$(CH_3)_2CH.COOH$	1·0196	0·00144
$(CH_3)_3C.COOH$	0·0909	0.000978

A similar decrease in the amount of ester formed is found if the complexity of the alcohol be increased while the acid remains the same throughout, *e.g.* when acetic acid is esterified with methyl, ethyl, isopropyl, and tertiary butyl alcohols. It is evident, therefore, that the cause of the decrease in the amount of ester formed is to be sought in the change in structure of the acid or of the alcohol. On examining the formulæ shown in the table, we find that in each case as we go down the table we are replacing a hydrogen atom by a methyl radicle. In other

[1] Menschutkin, *Ann. chim. phys.* [5], **20**, 229 (1880); **23**, 14 (1881); **30**, 81 (883); *Journ. Russ. Phys. Chem. Soc.* **9**, 316, 346 (1877); **10**, 278 (1878); **11**, 24, 345 (1879); **12**, 82 (1880); **13**, 564 (1881); **16**, 356 (1884); *Ber.* **13**, 1812 (1880); **30**, 278 1897); *Annalen der Chem.*, **195**, 334 (1879); **197**, 193 (1879); *Journ. Chem. Soc.*, **8**, 1532 (1906); Sudborough and Lloyd, *ibid.* **75**, 467 (1899).

words, we are exchanging a small light group for a large heavy one.

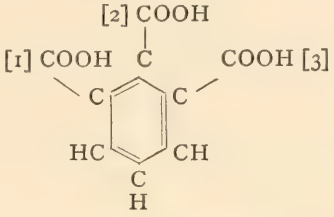
Let us next consider what takes place when an acid reacts with an alcohol. Obviously the hydroxyl group of the alcohol must come within range of the carboxyl group of the acid before any interaction can take place, since the ester is formed by the elimination of water between these two groups. Now, if we could interpose some barrier between these two radicles, we should hinder the esterification; and the more effective the barrier was, the less ester would be formed. Such a barrier is found in the methyl groups of the substituted acetic acids. According to the current theories of chemical action, a certain amount of free space must exist around the hydroxyl group before the carboxyl radicle can come within reaction range. The light hydrogen atoms are easily thrust aside by the heavy carboxyl group, and therefore the esterification of acetic acid is easy. When we replace the light hydrogen atoms by the heavier methyl radicles, however, the resistance to the entrance of the carboxyl radicle becomes serious, and consequently much less ester results. The following analogy may help to make the matter clearer: Suppose a man to be desirous of passing through a certain door, guarded by children. He would be able to pass because his strength would be greater than that of the guards; but if the children became men, his chances of passing the door would be very considerably reduced.

This *steric hindrance*, as it is called, has been observed in nearly every class of reaction; and there seems to be no doubt that the substitution of one group for another may influence the course of a reaction to an extent which seems quite out of comparison with the slight change in the chemical character of the substance which the substitution produces. We must now consider an application of this view to the question of vital action.

On Ehrlich's theory of antitoxins there are two sets of molecules in living tissue: those on the outer surface of the cells being concerned with the nutrition process, while those within are employed in cell metabolism. If the outer, or peripheral, molecules can be put out of action, the cell lacks nutrition and eventually dies. Ehrlich supposes that the peripheral molecules have active side-chains serving to anchor suitable molecules which may be carried past them; and in

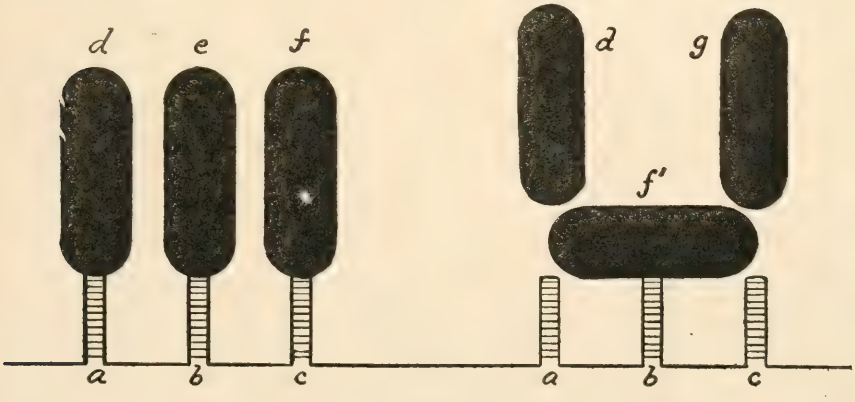
this way the cell extracts the necessary nutriment from bodies carried past it in the blood currents. These side-chains, however, may serve to anchor toxin groups as well as nutritive ones; and, on Ehrlich's view, when a sufficient number of toxin groups have been anchored, the nutrition of the cell may suffer to such an extent that the cell dies.

Schryver[1] has put forward a different view of what takes place. A concrete example will make the matter clearer, and for the sake of simplicity we may symbolise the cell by the benzene tricarboxylic acid shown below:



Here the active side-chains are represented by three carboxyl radicles. Now suppose that a molecule of aniline passes within the range of the central carboxyl group (2), and is seized and anchored by it. The presence of this large group will hinder the approach of other aniline molecules to the carboxyl groups (1) and (3), so that they will be temporarily put out of action until the first aniline radicle is disposed of.

We may represent the action diagrammatically in the following way:

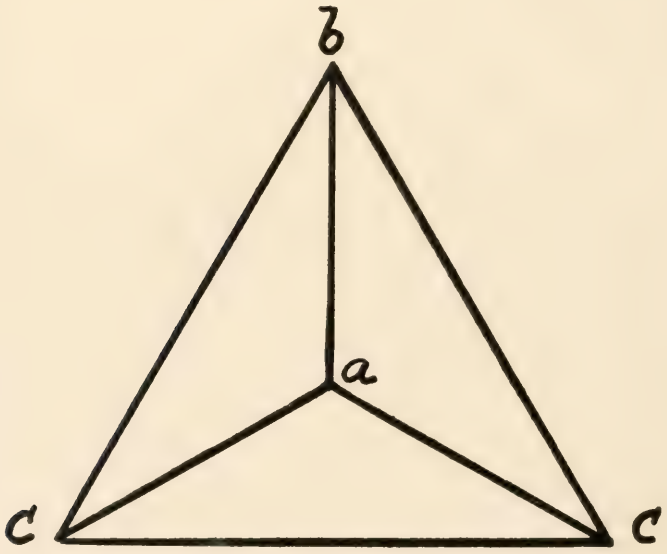


(*a*) FIG. 1. (*b*)

[1] Schryver, *Chemistry of the Albumens*, p. 183 (1906).

In fig. 1*a* the side-chains are represented by the unshaded parts *a*, *b*, and *c*, while the molecules of nutritious substance are represented by *d*, *f*, and *g*. It is obvious that the presence of the molecule *f* on *b* will not interfere to any extent with the action of *a* or *c*. This symbolises the normal action of the side-chains. If, however, the central side-chain *b* should happen to anchor the abnormally large body f^1 (fig. 1 *b*), the state of affairs would be quite different; for f^1 occupies so much room that the side-chains *a* and *c* could not come into play, and the cell would consequently be starved. On Schryver's view, then, toxicity in a tissue may be regarded as due to a steric hindering of normal functions.

Before concluding this article, some mention should be made of the relation between vital action and the production of molecular asymmetry. When in the laboratory we convert a compound $Cabc_2$ into another, *Cabcd*, which contains an asymmetric carbon atom, it might be expected that an optically active product would result. In practice, however, this does not occur; for instead of one antipode being produced, the final product is racemic. A consideration of what takes place in the course of the change from $Cabc_2$ to *Cabcd* will make clear the reason for this. In the substance $Cabc_2$, we are dealing with a tetrahedral arrangement of atoms like that shown below:



The two groups *c* are identical. Now, if the right-hand *c* be replaced by *d* we shall have one compound, while if the left-hand *c* be chosen for replacement we shall have the optical antipode. Since the optical antipodes are identical in chemical properties and differ physically only in respect to their crystalline forms, there is no reason why the dextro form should be formed rather than the lævo form; and there is no reason why one *c* should be replaced rather than the other, since they are symmetrically situated with regard to one another. It is, therefore, only natural that in one half of the total number of molecules the right-hand *c* is replaced by *d*, while in the others the left-hand *c* is chosen, the result being a mixture of the two antipodes in equimolecular proportions.

We may take it as a general rule, then, that from symmetrical substances only symmetrical products are formed in the course of our laboratory reactions. On the other hand, when we examine the constituents of living tissues we find that a very large proportion of them are optically active substances, so that at the first glance there appears to be a profound difference between chemical actions in the laboratory and those which are carried out within living organisms. At present those chemists who take an interest in the matter are divided into two schools. The one school holds that there is no fundamental difference between the chemical processes of vital action and the chemical processes of the laboratory; while the other school maintains that the question of molecular asymmetry sharply divides the two sets of phenomena. Up to a few years ago, neither view could call any experimental evidence to its assistance. The case of sodium ammonium racemate was cited by the "uniform" school as a proof of their case. This substance, if allowed to crystallise from its solution under certain conditions of temperature, separates spontaneously into two sets of crystals which, owing to the difference in the disposition of their hemihedral faces, can be separated by hand from each other. The upholders of the vitalistic theory of molecular asymmetry, however, pointed out that in order to separate the two vital action was necessary, since a human being was a vital agent. It is unnecessary here to enter into the details of the arguments employed on both sides; they are to be found in the correspondence in *Nature*,[1] and were chiefly theoretical.

[1] *Nature*, vols. 58 and 59 (1898-9).

The question appears to have been settled in a somewhat unexpected manner. Cotton,[1] examining the absorption of dextro circularly polarised light by copper ammonium tartrate, found that the two tartrates did not possess identical powers of absorption. Now, if light is absorbed by any molecule, some extremely delicate rearrangement of the molecule's internal structure must take place; for we cannot imagine that a vibration can be stopped without some energy being expended in stopping it or changing its amplitude. Therefore, in the case of the dextro and lævo forms of copper ammonium tartrate, more energy is being used up by the one form than by the other; and hence the intramolecular readjustment is greater in the one isomer than in the other. In other words, dextro circularly polarised light is an agent which favours one form of tartaric acid rather than the other. Now, Byk[2] has pointed out that light is circularly polarised by the surface of the sea, and that one variety of the circularly polarised light predominates on the earth's surface. This obviously furnishes us with an asymmetric agent whose application, as far as the earth is concerned, is nearly universal; and it seems not improbable that some such cause, acting under favourable conditions, may have given rise to a preponderance of a right-handed or left-handed form at one particular period in geological history. Until some active substance is actually synthesised by this method, however, the question must be regarded as, at least technically, an open one.

It should be noted that once the presence of an asymmetric substance is granted, the subsequent steps up to the present complex series of naturally occurring asymmetric forms become simple to understand. A very small quantity of an asymmetric acid, under suitable conditions, may serve to resolve any quantity of a racemic base without losing any of its peculiar asymmetry; while each portion of base resolved into its antipodes becomes a new centre for the resolution of racemic acids, which in their turn may serve to resolve new bases, and so on *ad infinitum*. The case is analogous to that of ordinary animal reproduction, since with each generation the reproductive power increases in geometrical proportion.

In conclusion, it may be pointed out that the accumulation

[1] Cotton, *Ann. chim. phys.* [7], **8**, 373 (1896).
[2] Byk, *Zeit. physikal. Chem.* **49**, 641 (1904); *Ber.* **37**, 4696 (1904).

of further data as to the action of stereo-isomers upon animal tissues is very desirable. Since a slight difference in structure may produce a great difference in the action of drugs, it seems advisable to begin by investigating those cases in which the structures of the bodies are identical, and the only difference lies in the special arrangement of the atoms. At the present time the data in this branch of the subject are only sufficient to show that the influence of stereo-isomerism is of importance; they are not full enough to enable us to draw any general conclusions.

THE PROPAGATION OF PHYSIOLOGICAL CHANGE

A PHYSICAL PROCESS

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It is a leading characteristic of living matter that it is readily excited by slight sudden changes in its environment. To these stimuli it frequently responds by chemical and physical reactions in which much more energy is transformed than was supplied by the exciting cause, in this way resembling all unstable structures and compounds. It differs, however, from these unstable bodies in that it rapidly returns to its original state, abstracting matter and energy from its surroundings to make good its loss—a process which can be repeated indefinitely. Nor is the word indefinitely made use of in any limited sense, as will be apparent when the processes of growth and multiplication are considered. Unstable when momentary changes are dealt with, stable when time is taken in larger units, living matter is usually spoken of as "labile."

Now when an attempt is made to penetrate the meaning of this state there are certain facts which always obtain a primary hearing for circumstances of purely chemical rank. In the first place many of these exciting causes lead obviously to chemical change, as in the case of muscle, from which, when excited, waste products trail away as definitely as the smoke and fumes from any chemical factory. In the second place there is no doubt that all the energy transformed in the body is liberated as a consequence of the oxidation processes by which its food material is overtaken. This statement has within recent years been placed in a position of almost absolute truth.

Explanations of both phases of this condition of lability have therefore most frequently been arranged in terms of chemical reactions. At one time we were invited to think of these vaguely as due to processes of assimilation and dissimilation,

anabolism and katabolism; no very certain limit being placed to the meaning of these terms. Alongside of the processes leading to the formation of an unstable and highly complex product were also processes leading to its destruction, and both sets of processes were characteristic of the normal resting state of living matter. Stimulation led to a new quantitative relation between the two, so that momentarily the destructive process was dominant. During the recuperative period following excitement the constructive process was dominant in its turn.

More recently considerations introduced by Ehrlich, as also the time relations of the oxidation process observed by Hermann, have served to modify and harden this view. It is on the one hand made clear that the destructive process need not be postulated as overtaking more than a certain fraction of the molecule, or, as it is expressed, no more than certain of its side chains. On the other hand also the constructive process can be imagined as repeatedly recommencing from a constantly surviving level of considerable perfection. Verworn has therefore brought to our notice a certain stable atom-complex, or nuclear group, to which more unstable side chains are linked under pressure of ordinary chemical and physical circumstance. In these and between these side chains perpetual change occurs, which is exaggerated and perhaps given a new direction by the incidence of stimulation. Every act of "life" therefore has its basis in the chemical changes taking place on the fringe and within the influence of these residual nuclear molecules. This at least if certain "enzymes" are allowed to play a part less definitely assessed, and take a place in the molecule less definitely assigned.

To satisfy the intimacy of intracellular life the conception has been tentatively extended by a hypothesis first boldly introduced by Pfluger. The residual atom-complexes are linked together to form a giant nuclear molecule which occupies a great share of the space within the cell, as for example the whole of that process of a nerve-cell known as the core of a nerve-fibre. In this way we have in front of us a schema which clearly illustrates the conception that "life" is primarily dependent upon chemical structure, and that all the expressions of life are the outcome of chemical change. This conception has indeed been welcomed as serving usefully to link together many

experimental facts. In the first place those facts upon which it was based, the storage of oxygen within the cell in chemical combination alongside of oxidisable material to which it is finally handed over. In the second place such instances as those in which minute traces of specific chemical materials modify the life and activities of the cell. In this latter case the concept has justified its existence by indicating fruitful lines of experiment. Its influence has also been clearly felt in further elucidating the importance of oxygen not only to life, but also to function.

We must ask, however, whether no position of importance should be accorded to states and changes of a purely physical kind. Surely these also play their part within the cell. Their influence upon extra-cellular material is often paramount, and it is perhaps best by a consideration of this influence that their case may be introduced. Let us for example consider a rod of cartilage. Here cells are situated in a mass of tough material which they have manufactured. Unlike their epithelial cousins situated on the surface of the body, they do not pass their manufactured products on to a surface from which in the course of events these are swept away. The cells are therefore separated by a greater amount of material, which first oozing from them as a viscid mass no more rigid than its source, then sets into the tough elastic substance to which the cartilage owes its physical characteristics and its sole use. Now who can deny the probability that this process of "setting" is due to stimulation provided by the stresses and strains to which the exuded material is at once subjected? We thus get a picture of this extracellular material undergoing a change of physical state of functional importance, and that as the result of excitation. Again, as the cartilage plays a frequently repeated part in the stresses and strains to which the limb is subjected by muscular action and external pressure, certain points within it are selected as the foci through which resultant forces pass. These most probably are the "centres of ossification." The forces in action arrange the cells and matrix in columns radiating from this centre. The stimulated matrix continues with its change of state, the colloid material passes from the condition of a homogeneous jelly into one in which there is a precipitation of denser "calcified" material from a more simple solution readily removed; condensation and liquefaction. Is this a

chemical change resulting from the exudation of a new corrosive substance from the excited cells, or is it a physical consequence of repeated pressure upon the homogeneous jelly? It is clear that the mass primarily stimulated is the jelly, which from its consistence must be held to protect the cells enclosed within it. Again, the irruption of bone-forming cells takes place, made possible by the liquefactive change. Each one of these new cells secretes an exudate which then "sets." The directions taken by the fibres precipitated in the setting bone-matrix at once suggest the notion that they are the result of the stresses and strains to which the material is subjected. Calcium salts also make their appearance passing from a state of solution to be precipitated as granules. In the case, then, of bone-formation it is again the change of physical state which at once claims our interest. Now it may be objected, that there is no proof that these changes are not of chemical rank, perhaps even attended with an output of waste products. However, even if that possibility be admitted, the contrary hypothesis is seen to be at least as admissible, and therefore to require definite examination.

But if a case can be made out for the examination of such possibilities when dealing with extracellular material, the same possibility must also be introduced within the limits of the cell. The difference between similar changes within and without the cell may be no more than a difference of opportunity and advantage. Outside the cell the sole sources of energy are those provided by stimulation and the heat of the circulating solutions of the body. The cell has the advantage here. Inside the cell recovery may thus be more usual than outside of it. Within the cell, as for example in the musculature, is the source of heat production whence the heat of these circulating solutions is derived. Within the muscle-fibre itself this chemical source of energy may play no greater part in many important internal processes than is played by the heat of the forge in the production of steel. If the muscle distributes heat to other tissues of the body which is made use of in this way, what limits are to be set to its own participation in similar advantages? It is a possibility often lost sight of, but none the less important, that the source of energy within the muscle may possibly be responsible for physical states, *for physical stores of potential energy*, the disturbance of which in their turn may give rise

to a development of heat. Heat so produced is to be traced finally to the combustion of food material as surely as that directly produced by the occurrence of concomitant chemical change.

So far I have done no more than consider the possibility that physical state and change may be of importance in intracellular change. Let us consider a case where they must of necessity be introduced—as for example in the secretion of water as sweat at a point upon the surface of the skin. Below this surface there extends a long tubular pocket lined by epithelial cells. These cells are suddenly aroused from a state of rest by the arrival of a nervous impulse dispatched from the central nervous system; after a short delay water wells from the mouth of the pocket on to the skin. Whence does this water come? Certainly not from the side links of any "biogen molecule" within the cell. The water has indubitably been drawn through the cell from the solutions bathing its internal surface. The cell has acted as a pump in which valves give a direction to the work performed. Now how is this to be dealt with if the physical arrangements of the materials forming the cell are not to be placed in the foreground as matters of importance? Discuss these arrangements and it at least becomes possible to conceive a line of experimental approach to the phenomenon.

Let us for a moment suppose that, as is most probable, the internal and external surfaces have characters of a different kind. In some epithelial cells such differences can be seen. In all, even including the nerve-cell, such differences must be inferred. Let us suppose that this cell, set upon the surface of the body, is in the habit of passing some of its waste products, as for example carbonic acid, not back into the solutions of the body, but out on to its external surface. What more probable? But then, if so, we have only to imagine that our exciting nervous impulse quickens up the chemical changes occurring within the cell and so gives rise to the production of carbonic acid. These new molecules, added to the physical value of the cell as a mass of molecules in a state of solution, are the cause of an increased osmotic pressure which is sufficient with the differences postulated between the cell surfaces to account for the passage of water out into the pocket of the little gland. Here we have been forced to think of the matter within the cell as a solution,

of a chemical change as merely adding to the number of molecules in solution, of the cell limits as permitting or restraining the motion of dissolved material. None of the important activities underlying these terms are made obvious by the contemplation of "biogen molecules."

Let us examine an instance a grade more complex. The salivary glands are formed of similar pockets, from which on the arrival of a nervous impulse water again gushes out on to the surface of the body containing in solution organic and inorganic matter. The same explanation will temporarily cover the output of water. But why these other substances also? Now there is no doubt that most of these other materials have lain within the cell long before the arrival of the nervous impulse, having been manufactured during hours of rest from secretion. They are now merely washed out in the rush of water. In addition to the chemical work done on receipt of the impulse we have here to consider specialised chemical work performed quite independently of this, such as is done by gland-cells to which no such impulses come. Is it of advantage to consider the molecules engaged in the one change and in the other as necessarily the same? Is it not simpler to think of molecules of diverse kinds in solution side by side but undergoing a different cycle of change with intensities that reach their maxima at different times? We have been compelled to introduce the concept "solution" to explain the transit of water. There can be no doubt now, as the result of manifold experiment, that this concept has to be introduced in case of every cell; nor even any doubt, to make the matter physically more complex, that the variations of phase within these solutions undergoing change with every kind of alterations in physical circumstance have all to be taken into consideration as modifying the activities of the cell, and therefore as variable physical states of functional importance.

Now it may be said that, after all, these instances have done no more than attribute important results to chemical change as the primary source of energy directly involved in the processes considered. The carbonic acid production has been dealt with as the source of the change. But what if we select as our new molecule adding to osmotic pressure not carbonic acid, so obviously the outcome of an oxidation process, but some inorganic salt? In the case of the salivary secretion certain

experimental facts render a consideration of this possibility necessary. Here the chemical side is not so obvious, since we may suppose these molecules to have been pre-existent within the cell, and to be liberated not from a position of chemical combination, but from some position of physical restraint on arrival of the nervous impulse. This is a possibility with an important distinction. The whole sudden energising of the cell is made to take an entirely physical form. In this case, however, the chemical side must not be lost sight of. We must suppose that, during its rest from secretion, the chemical energy of the cells was utilised in producing this physical condition of restraint, and so feeding a secondary source of energy conveniently available at the moment of stimulation.

And now, having prepared the way by means of allegory, I would turn to the specific instance which I am more concerned in protecting from this purely chemical conception of function. If living material is at one time stable and unstable, is labile, where is this fact more obvious than in the case of nerve? Excited by almost every slight change of environment to a display of function and therefore most unstable, but recovering so rapidly that within one five-hundredth of a second it can be provoked to an exactly similar change of state—a process which under favourable conditions can be repeated from dawn to dewy eve without giving rise to any trace of fatigue. Pancreas cells may be unexcited to their specific function save on the addition of certain specific chemical materials. Mammary-gland cells may preserve a similar scorn for fleeting change. In them obvious chemical work is done, and the chemical composition of the media in which they lie is their main concern, of which they are not oblivious; but of their extreme lability what proof have we? Astonishing pictures of exhausted cells indeed form evidence for an opposition. Turn to nerve-fibres and the facts are curiously reversed. Most stable and yet most unstable, "labilissimi," what proof have we of the primary importance of their chemical constitution and its changes? Practically none. I shall escape impeachment for this statement. The main fact is so clear notwithstanding some slight evidence to the contrary. Thus Waller has in most ingenious fashion shown that prolonged stimulation leads to just such a modification of conduction as is producible by carbonic acid, but not unproducible

by other factors also. Bethe has shown that prolonged stimulation is followed by an alteration in staining capacity with certain basic dyes, a circumstance which may have no more meaning than an alteration in physical state. It is true that this absence of chemical evidence may be ascribed to the minute quantity of change involved, and to the swift flight of the nervous impulse.

It is no doubt true that the maintenance of life in the nerve-fibre is dependent upon chemical factors. As is the case with all intracellular material, the continuance of its function is ultimately dependent upon a complex of chemical and physical states to which the cell-nucleus, nutriment, oxygen, and the removal of waste products such as carbonic acid are essential. Doubtless, too, this complex is affected by narcotics in some cases, in a manner to be assigned to the inhibition of certain essential chemical processes. No doubt also drastic interference with this complex may produce an abnormal physico-chemical state in which symptoms of fatigue become obvious, as in the instance of the effects of aconitine observed by Waller, chloroform by Garten, lack of oxygen by Frohlich. But here we have our fingers upon the very acme of lability. This is the tissue from which many of the conceptions of lability of living matter are derived. It is significant that here of all places we should have to hunt so desperately for instances of chemical change. There is, then, excellent reason why, on a basis of experimental fact, nerve should not be used in illustration of the value of any purely chemical concept of function.

Thus that rapid propagation of physiological change from point to point which is the leading function of nerve, but is by no means confined to nerve, is doubtless always due to the conveyance of a physical change. The train of gunpowder is apparently a simile to the contrary, but I believe I am right in insisting that in this case the explosion of each segment in turn is due to a rise in temperature. That physical factors are alone responsible for the similar excitation of each successive piece of nerve has been laboriously proved by a study of the action of every admissible form of stimulus. Efficient physical forms of stimulation are, the incidence of light, a rise of temperature, a slight mechanical shock, pressure, a sudden fall of electrical potential, sometimes a fall of temperature, sometimes a rise of electrical potential, sometimes the removal of

pressure. Every sudden change in physical environment is liable to stimulate nerve. Efficient chemical means are all illusory. Only such chemical reagents as have a capacity for indirectly producing physical change are capable of stimulating. Their effects are then in proportion to the physical change which they are capable of producing, as has been well shown by Matthews. Solutions of electrolytes produce electrical effects. Solutions of varied concentration cause variations in the water content of the nerve. Concentrated solutions by concentrating the electrolytes in the interior of the nerve give rise to self-stimulation. The transference of the excited state from point to point of the nerve can therefore be assigned with certainty to physical change, and this no matter whether the disturbance at each point thus affected involves chemical change, such as the decomposition of a carbohydrate or a fatty side chain, or physico-chemical change such as the disruption of some adsorption complex, or purely physical change such as the conferring of new motion upon matter in solution. There is, in fact, no experimental datum which would enable us to think of any other factor than physical change as responsible for the transmission of the excited state from point to point. We are, therefore, debarred from accepting in this case many of the mechanisms which have been suggested, such as, for example, the transference of an oxygen atom from side chain to side chain of an excited giant molecule.

Compelled thus to retreat to physical change alone, there can be little doubt as to the nature of the physical change which is responsible. Most careful experimental inquiry has failed to obtain any evidence of heat-production such as occurs in the train of gunpowder. As to the occurrence of an electrical change of very considerable magnitude, such as has been most beautifully measured by Gotch and Burch, there is no question. This in fact is the only kind of change which has been found to accompany the transit of a nervous impulse. The point, therefore, which has seemed long to Hermann and others of capital importance should be stated boldly. *No matter what may be the complete change at each excited point, its transference from point to point is accomplished by electrical agency.* To this statement the absence of any temperature change enables us to make an important addition. This excited state which is propagated by electrical change is certainly not a chemical

process such as is attended with a consumption of oxygen, nor with the transit of oxygen from less stable to more stable combination. And this is equivalent to saying that, whereas oxygen may play a considerable part in the maintenance of the normal state of nerve, it plays no part in its function. We are obliged, therefore, to consider the case of nerve apart from the case of muscle, where each functional display is attended with a production of heat and a discharge of carbonic acid. But is this statement as true as it at first sight appears? In muscle function there are two clearly separable phenomena, the propagation of an electrical change and the consequent contraction. The propagation of electrical change is undoubtedly a process of the same rank as the process studied in nerve. With regard to this moiety of muscle function wherein muscle resembles nerve, there is likewise no evidence of any production of heat or output of waste product. The electrical change is over before the occurrence of that functional display which is usually thought to be associated with these factors. In the case of muscle, when acting as nerve, the facts are obscured by a later exhibition of another function. In the case of nerve itself the facts are clear. There is nothing but an electrical change observable.

It is not marvellous in view of such evidence that investigators have been found bold enough to plan a line of experimental attack upon the mysteries of nerve function, based primarily upon the assumption that the materials present in nerve are important solely as conductors, insulators, dielectrics. This is a very different assumption from that underlying the "biogen molecule," and yet in this case it has proved of the utmost value. If the purely physical concept of nerve function is finally set on one side, it will be set on one side as the result of evidence collected upon these lines. Some of this evidence has favoured such a concept, some of it has served materially to limit its range. The peculiarities of the electrical conductivity of nerve have been closely studied, sometimes deliberately, sometimes as a series of data which would one day acquire biological interest in connection with the characters of protoplasm. Both sets of workers have used the same methods. An electrical current is passed through a nerve and data are collected from the "polarised" region as also from the extrapolar stretches. For instance, in the anodal extrapolar region

each point nearer to the pole acts as if at a higher potential to points more remote; in the kathodal extrapolar region near points act as if at a lower potential than points more remote.

Now, when an attempt is made to explain these facts, there is no doubt but that we must first consider all the peculiarities of the complex arrangement of electrical conductors represented by the nerve-trunk. Until that is done few will listen to the appeal: let us be simple, we are studying life. Physical models built of materials of different conductivity have been constructed to illustrate the peculiarities found. These models form a physical scheme for a simplified conception of the arrangements of conductors within the nerve-trunk. The inquiry is then pushed further. Can electrical impulses be propagated along such models? Certainly. Well then, are we to consider the nervous impulse as a phenomenon of a type akin to these? Boruttau, assiduous worker upon the electrical phenomena of nerve and upon such illustrative models—that is to say, an examiner of both sides of this question—answers in the affirmative.

Now, before deciding the extent of the reliance we will place upon this answer, we must note an important fact. Nervous impulses, whatever their essential nature, are propagated by electrical agency. They are also propagated along contiguous fibres in different directions without in any way modifying one another. Nerve-fibres therefore represent isolated conduction, and, as we have said, this entails electrical insulation. That this insulation is by no means perfect follows from the fact that electrical currents can be made to traverse nerve-fibres, and also that the electrical phenomena occurring within the fibre are demonstrable upon its surface. It might easily be shown, however, that this imperfection as revealed in both of these facts is of such a kind as to confirm the main statement when put in a slightly different form. The sheaths of nerve-fibres profoundly modify the motion of electrolytes. It follows therefore, no matter what may be the nature of the excited state of nerve, that the study of the electrical conductivity of nerve must be expected to develop information such as will be gained from the examination of any set of imperfectly insulated conductors. The core-model can be foreseen, and its invention cannot be at once accepted as revealing essential facts. It is not enough to have become acquainted with the insulation of the

central conductor. Before committing ourselves to any dogma it is necessary to have studied the character of the core. We must, in fact, find data upon which to consider the possibility that the nervous impulse is no isolated phenomenon, but one that has its analogue in the conveyance of excitation from point to point within all kinds of cell structures where insulation is neither discoverable nor theoretically required. Boruttau has appreciated this necessity. He has transferred the facts of the core-model to the central core. But for this transference he has, in my opinion, no warrant. If the core of the individual nerve-fibre does really possess a structural arrangement similar to that of the core-model composed of its several parts, that fact has yet to be demonstrated. The facts elicited so far are of a different order. Boruttau has, so to speak, abandoned a consideration of the sheath without omitting the very important facts for which this structure is responsible from the experimental data made use of to present the case in this new sheathless form. On this, and on other grounds also, we for the time being fight shy of this core-model theory of nerve function.

Do considerations such as this, then, drive us back into the arms of the biogen molecules? Certainly not at present, since the needful factors seem at least in great part physical. The core has still to be studied as a conductor of electricity, that is to say, as a solution of electrolytes. What are the electrolytes of nerve? How are they distributed within the nerve-fibre? How is the motion of electrolytes which takes place within the core during the conduction of a nervous impulse to be explained?

Now if at first sight it seems absurd to treat of this core, this strip of protoplasm which is responsible for so much, as a solution of electrolytes, let us remember our treatment of the case of the cells in the sweat-gland and in the salivary gland. In putting nerve material in such a category we do nothing new or unexpected. This criterion "solution" is one to which every cell has to be compared, and from it much information illuminating the basis of function has already been obtained. The general considerations which entail this treatment are present in nerve as elsewhere. Thus the core exerts an osmotic pressure upon the surfaces inclosing it, and this pressure is normally balanced by the pressure of the solutions outside. Alter the character of these solutions ever so little and this is at once seen.

Immerse a nerve-trunk in water or in dilute solutions, it becomes turgid, and in consequence as rigid as a stick. Immerse it in concentrated solutions, it loses in weight and becomes abnormally crenated and limp. Watched under the microscope individual fibres may be seen to undergo corresponding change. Passing in review the materials in solution within the core it is at once obvious that, as in the case of other tissues also, the number of molecules of simple bodies like the inorganic salts is overwhelmingly great in comparison to the number of the huge protein molecules with which the concept "biogen" is inextricably associated. Experiments of this type are of such a nature as to give us some knowledge of the number of molecules within the core, a number to which the inorganic salts present contribute a share so great that the contribution of other matter is negligible.[1] From such experiments there is promise therefore of obtaining a quantitative value for the inorganic salts, and that is almost equivalent to the value of the electrolytes within the core. Here, then, is a road to the knowledge immediately required to fill the gap in the data requisite for a proper discussion of the core-model theory. It is unfortunately the case, however, that this road has been shown not to be a high road. The information obtained is not of such direct value as it seems, since it has been found that a balance is not necessarily obtained by equalising the salt-content of the internal and external solutions. Such knowledge, then, is of value, but is apprised as only one of the items necessary to a complete understanding of the case.

We expectantly turn, therefore, to another method which promises to provide further information as to this core in so far as it can be treated as a solution of electrolytes. An electrode placed upon the core exposed at a cross-section of a nerve-trunk is electrically negative to a similar electrode placed upon the uninjured longitudinal surface. This fact is with great probability to be assigned to a difference in the solutions present in these two situations, and to the nature of the membrane formed by the sheath of the fibres, which limits the diffusion capable of taking place between the solutions in the interior of the nerve-trunk.

In the concentration cell so formed one of the solutions

[1] Carbonic acid molecules are not considered in this case, since the surfaces are permeable to them.

is accessible, its character well known; this is the external solution or lymph, which surrounds the fibres and bathes their longitudinal surface. Modifications in this external solution produce modifications in the electromotive force of the concentration cell. Such modifications have been carefully studied, and it has been shown that they are quantitatively consistent with this assumption made as to the nature of the source of E.M.F. The external solution being varied, the internal solution is found to behave as a solution of electrolytes of such constancy that the data obtained from one nerve by one variation of the external solution are capable of accurate contrast with the data obtained from another nerve with another variation. The facts are so definite, indeed, that it is possible in this way to determine the concentration of a solution, by placing it upon the surface of a nerve instead of the normal external solution and observing the alteration produced in the E.M.F. of this concentration-cell. Here, then, is another road along which to obtain a knowledge of the internal solution of electrolytes. Given one condition it can obviously be made a high road to their quantitative determination. If the specific nature of these electrolytes were known, then that strength of their solution which would reduce this E.M.F. to zero would coincide with the strength of the internal solution. In the experimental work done in this subject this point has been realised. There is evidence, recently strongly reinforced by the use of microchemical methods introduced by Macallum, that the electrolyte concerned is potassium chloride. Doubtless this point, its importance once realised, will be settled by such direct determinations of the salts in nerve as is now being undertaken by Alcock. It is significant of the times and of the ideas which have been introduced in competition with such concepts as "biogen molecules," that so much effort is being expended upon the decision of this question. Assuming this internal electrolyte to be potassium chloride, then it has been shown that the solution present within the nerve-fibre is of such an extraordinary concentration that it is impossible to think of such a concentration as normally present there. Here then we have a handsome paradox, but one for which there is possibly a clear explanation.

When nerve-fibres are injured as by a cross-section, they are excited. If it is assumed that the excitation is a fatal one,

from which the fibres do not recover, there is then present at such cross-sections a stationary excitation. Now we have shown that the transference of excitation is a matter definitely to be set on one side as due to an electrical agency—that is to say to a motion of electrolytes. Since we must think of this motion of electrolytes as produced by an alteration of the character or quantity of electrolytes present at an excited point, we may expect to find at a fatally excited point the new or additional electrolytes thus known to be characteristic of this state.

There is no evidence that the nature of the electrolytes is new. Here we are down upon an old bone of contention. It has been suspected that a decomposition process occurred at such injured points attended with an output of carbonic acid and waste products of a similar kind. There is, however, no acidity to be detected. If there were, the amount necessary to account for the phenomenon would have to rise to a value instantly detectable. This is shown by the fact that this injury current, which may be modified by alkali as by any other electrolyte, is not annihilated by a value of caustic soda solution below 0·8 per cent., and that solutions of hydrochloric acid may equally well be used for this annihilation. Place this beside the fact that it is possible to identify the additional potassium evoked by the injury by microchemical means, and it seems certain that injury produces not an electrolyte of a new character but an additional quantity of such electrolytes as were already present. A study of the injury current therefore may be taken to have revealed the existence of a solution of extraordinary concentration in the excited region of the nerve-fibre. It seems obvious that excitation may modify the strength of the solution present in one of two ways—either by withdrawal of water for combination with some more solid material not to be reckoned as part of the "solution," *e.g.* in a solid phase, or by release of potassium salt from under cover of some such solid phase into the quantity of material to which the general character of "aqueous solution" is due, or from some state of chemical combination.

The terms in which the last sentence are couched are the result of a microscopical study of the core of the nerve-fibre. It is impossible long to pursue a study of nerve-fibre structure without being impressed by the colloidal character of the

solution within the core. On immersing fibres in solutions of different concentrations attention is at once drawn to the precipitations and re-entrance into a state of solution of the colloid material present. Such variations have also been observed by Höber in nerve-fibres treated with solutions of electrolytes, and have been inferred as of probable occurrence by Matthews, Greeley, Loeb, Lillie, and others. Nor is there any need to vary the character or concentration of the surrounding solution to observe these effects, since a distribution of varied states of colloidal solution is discoverable in nerve-fibres immersed in the solution usually first made use of, such as "normal saline" or "Ringer," solutions somewhere about the concentration of a decinormal solution. The states thus observed have a definite relation to injury and to the injury current which arises from it. At the cut end, the source of this current, there is some precipitation of colloid matter from solution; this portion is limited by a stretch of limpid solution, and this is again succeeded as we reach kathodal points, where the current is leaving the nerve-fibre to enter the surrounding solutions, by successive tracts showing greater and greater degrees of precipitation.

But this is an observation pregnant with suggestion, since the conditions present at "kathodal points" are as of great an interest as those present at the injured region. If there were hesitancy in postulating something of the nature of excitation as influencing the conditions due to injury, there can be none in case of the kathode. The institution of the kathodal condition has been shown to be the cause of that excitation which follows the admission of an electrical current into a nerve. During the closure of the current the whole region of the kathode is in a state of increased excitability. It is significant, therefore, that at such points there is again a visible alteration in the core. The importance of this fact is enhanced by microchemical proof that in this district also there is present a solution of a potassium salt of much greater concentration than that to be found in any other part of the nerve-fibre except the region of injury. There is therefore some basis for the statement, that *at every excited point there is a coarser aggregation of colloid material, accompanied by the appearance of a new quantity of potassium salt in a state of simple aqueous solution.*

Apparently, therefore, the facts discoverable under these

headings of "injury" and "kathodal state," and the circumstances inferred from this as characteristic of excitation, are of the same order as those observed as a consequence of the excitation of extracellular material—as, for example, in the case of bone matrix, in which the setting of the matrix was attended with a demonstration of calcium salts.

It is necessary to explain at this stage an omission, which to the expert may seem of much account, namely, the absence of any reference to the finer details of the minute structure of the core. Histologists, whose views of structure are too frequently obtained from tissues altered by the precipitating effects of "fixatives," describe in this core long lines of a more refractive material which run parallel one with another and are separated by and surrounded with material of a simpler kind. The critic may say that the considerations which have taken us within the core should have taken us further. The point assumes importance since from several sides these neurofibrils have been accredited with the functions of the fibre. I have myself made theoretical use of such structures, but have been compelled to abandon them in consequence of a prolonged acquaintance with the appearance of nerve-fibres immersed in the fresh state in simple saline solutions. Neurofibrils are not seen under such conditions. This being the case, their admission into the summary of experimental evidence is hardly justified. It will be remembered that in the case of bone-formation fibrils are precipitated in the material as it sets, and that their arrangement is possibly assignable to forces in action at the moment of setting. It is possible that neurofibrils are similarly formed. If so, it is also possible that they are formed at a time when the setting of the colloidal solution of the nerve-fibre has attained a degree not arrived at during normal functional life.

Here at last, at the end of the evidence, one feels the demand for a constructive policy to guide further experimental work. If biogen molecules and "ion proteids"—the latter representing a concession, it is true—obscure many points of physical interest in the structure and function of nerve-fibres, and if the core-model theory is set on one side whilst a debate is arranged as to the nature and meaning of neurofibrils, what conception can be placed in their stead? Is there any "opening" along which the game can be further played with as much success as along

the openings thus discredited? This is a claim which I have ventured to satisfy.

Let the strip of protoplasm forming the core of the nerve-fibre be thought of, not as a homogeneous mass of similar molecules, but as a *solution* in which co-exist molecules of very different sizes and kinds. For simplicity let us fix our attention upon two kinds of molecules exhibiting these differences in their utmost extreme—one kind large colloid molecules tending to form aggregates, the other kind minute inorganic salt molecules and ions mutually avoiding one another but tending to be drawn into association with colloid aggregates. Imagine also that a certain average size of aggregate represents the normal condition of colloid solution in the nerve-fibre, but that departures from this average occur as a consequence of physical change or stimulation. The observation of precipitates at excited points justifies the hypothesis that an increase in this average size is a characteristic of excitation. Now let us suppose that these aggregates or solid phases, or—less correctly, but offering a readier picture—solid particles, attract the salt molecules to their surfaces, so that layers of a condensed salt solution are found thereon. It follows that, when excitation takes place and the number of solid particles is diminished, they in this new condition must offer a smaller total surface for the retention of such a condensed solution of inorganic salts. As a consequence a new mass of inorganic salt will have found its way into the general bulk of aqueous solution surrounding the colloid masses. We thus obtain a picture of the excited state in a form which satisfies all the experimental evidence, and the picture at the same time lends itself to a clear representation of the mode of propagation of the excited state—*i.e.* nerve impulse. To ensure the propagation of such a state in the manner observed in nerve, all that is necessary is to postulate that the exciting negative anion of the inorganic salt present should have a greater velocity than the positive kation. The salt is unmasked, it diffuses, the next segment is rendered negative, desolution accompanied by the unmasking of a further quantity of salt in this new segment, further diffusion, etc., etc.

Now if I am asked at what rate this change would be propagated—and this is a question of great importance—unprovided myself with more than vague uncertain murmurings I deliberately steal another's thunder. W. Sutherland

has conceived a physico-chemical explanation of the nature of the state of colloid solution, and of the nature of the nervous impulse. The molecules capable of entering the state of colloid solution are possessed of pairs of unsatisfied valencies carrying equal quantities of electrical charge of opposite sign. By reason of this quality these molecules can unite with one another to form giant molecules in which the original units are seen as "semplars" joined end to end or side to side, forming a long frame, around which and in the interstices of which the solvent lies. These giant molecules, and the core of the nerve-fibre is one such, being elastic respond to a shearing strain by the transmission of motion along the mass of the molecule. This transmitted state represents the nervous impulse, and at first apparently by a purely mechanical conception. But in the propagation of this strain opposite electrical charges are supposed in each segment of the molecule to be moved one upon the other. Upon such a basis Sutherland has worked out the probable rate of transmission of such a process, and finds it of the same order as the transmission rate of the nervous impulse. To me it seems that the mathematical treatment of this hypothesis involves considerations of exactly the same rank as those involved in the hypothesis I have advanced. The alteration supposed to occur in the colloid aggregates compares with the molar charges assumed to occur in the framework of the giant molecule, and there is the exactly analogous displacement of electrical charges, and in both cases that is all.

Should Sutherland's conception of the nature of the nervous impulse, or should mine, appear too bald or too far removed from considerations of biological rank, I would suggest that this function of transmitting change is of all the functions of living matter the most widespread and the most simple. It is probable that a similar change is transmissible within the limits of every cell in the body. This fact—and I would make bold to say that it is a fact—is frequently lost sight of in admiration of the complex results obtained as a consequence of the transmission of these changes into districts where more complex happenings occur. The conduction of nervous impulses is sometimes discussed side by side with the precise value of states of consciousness, although there is no evidence that the actual process by which change is propagated has altered in the course of development from the protozoon to man.

THE YEAR'S VERTEBRATE PALÆONTOLOGY

BY R. LYDEKKER, F.R.S.

THE following article is written on very similar lines to the one dealing with the same subject in this journal a year ago; and the introductory remarks in the latter will in the main apply in the present instance. It may, however, be well to repeat the statement that the publications referred to do not (and from the nature of the case cannot) represent anything like a complete record of the year's work in the palæontology of vertebrates. They are, in fact, merely the more important of those which have come under the writer's personal notice up to the date of sending the proof of the article to press. The opportunity has been taken to refer to a few papers published in 1906 which had not come to hand when the article for that year was compiled.

As was the case last year, there appears to be no startling or epoch-making discovery in this branch of palæontology to record; although a large amount of valuable work, either in describing new forms, or (which is at least equally important) adding to our knowledge of those already known to science, has been accomplished. From the standpoint of geographical distribution, the most important event of the year in the present department of science is undoubtedly the discovery of remains akin to the golden moles of Southern Africa in the Tertiary rocks of North America; a discovery which largely aids in explaining the anomalous distribution of this and the kindred families of the Insectivora.

Commencing with papers dealing with stratigraphical and faunistic palæontology, reference may first of all be made to one by Prof. H. Osborn, published in the *Bulletin* of the American Museum of Natural History, vol. xxiii. p. 237, on the Tertiary mammalian horizons of North America. Although confessedly a preliminary introduction to a fuller work, this paper gives much valuable information with regard to the

correlation and geological ages of the various beds; a noticeable feature being the introduction of diagrammatic sketches of typical local sections in the Rocky Mountain basin and the Bad Lands of Nebraska and Dakota, by means of which the equivalence of the various strata can be seen at a glance.

Closely connected with the foregoing is an article in the May number of *The American Journal of Science*, by Mr. F. B. Loomis, on the probable mode of origin of the Wasatch Eocene deposits. The relative scarcity of fish-remains forbids, in the author's opinion, the view that these beds were deposited in lake-basins. Nevertheless the occurrence of remains of crocodiles, freshwater terrapins, and fishes in sufficient numbers to make up 10 per cent. of the whole fauna, would be very remarkable in strata of æolian origin; and the presence during deposition of a certain amount of water seems therefore to be essential. It is accordingly suggested that the Wasatch beds were laid down on plains subject to periodical inundations; confirmation of this being afforded by their lithological constituents.

Californian cavern exploration has been continued by Mr. E. L. Furlong, who in a note to the March number of *Science* communicates the results of a preliminary examination of a cave near Auburn. The remains found included those of the ground-sloth *Megalonyx*, as well as of pumas and horses; but no traces were discovered of the extinct ruminants *Euceratherium* and *Preptoceras* characteristic of the Shasta caves explored by the same gentleman a few years ago.

In a paper published in the *Annals* of the Carnegie Museum, vol. iv. No. 1, 1906, Mr. O. A. Peterson describes a number of new mammals from the Miocene of Nebraska and Wyoming. Several of these belong to the group of oreodonts or merycoidodonts (the "ruminating hogs" of Leidy), but there is also a primitive camel, as well as a dog-like carnivore of the genus *Amphicyon*. The Miocene fauna of South Dakota has occupied the attention of Dr. W. D. Matthew, who has published the results of his investigations in the *Bulletin* of the American Museum of Natural History. The contents of this paper are noticed later.

In Europe Dr. Max Schlosser, in the *Neues Jahrbuch* (1907, vol. ii. p. 1), has given descriptions of fossil mammals from the Pliocene of Spain, with observations on the line of division

between that epoch and the Miocene. A similar service has been accomplished by Mr. F. Roman (*Comm. Geol. Portugal*, 1907) in regard to the mammalian fauna of the later Tertiary strata on the right bank of the lower part of the Tagus valley. In addition to remains of *Mastodon*, *Hipparion*, etc., the author has described those of an apparently new species of rhinoceros. Notices of later Tertiary mammals from Hungary will be found in a paper by Mr. W. Güll, and others, published in the *Mitteilungen Ungar. geol. Anstalt*, vol. xiv. p. 283. Similar brief mention will suffice for a paper by Mr. A. Zdarsky on the Tertiary mammal fauna of Eibiswald, published in the *Jahrbuch* of the Austrian Geological Survey (vol. lvii. p. 437).

A work of an altogether unique type is Mr. Charles Depéret's *Les Transformations du Monde Animal* (Paris, 1907). Its main object is to discuss our present knowledge of the laws regulating the modifications of animals, from the date of the first appearance of life on the globe to the present day. After a preliminary review of the rise of modern ideas with regard to evolution, the author discusses the variability of species in space and time, the constituent elements of phylogenetic "trees," the causes of the extinction of species, the formation of new types, and, finally, the important *rôle* played by migration in the evolution of faunas.

During the year the vertebrate fossils of the Fayûm district of Egypt have attracted American collectors ; and to the October number of *The Century Magazine* Prof. H. F. Osborn contributes an illustrated article describing his experiences while in search of such remains, with remarks on the nature and origin of the fauna and their bearing on the geographical distribution of mammals. Among the illustrations, attention may be directed to restorations of *Arsinöitherium*, *Hyænodon*, and *Zeuglodon*. In Eocene times the Fayûm, in the author's opinion, was a savanna-country, partly open, partly covered with scrub, and partly with forest; the temperature being much the same as at the present day. That Africa (then much less extended to the north than at the present day) was the home of the ancestral proboscideans, sea-cows, hyraxes, and probably hyænodonts, Prof. Osborn is convinced; but the absence in the Eocene deposits of remains of primitive hippopotamuses, ruminants, horses, and rhinoceroses, leads to the further inference that "none of these quadrupeds had as yet reached

Africa; that they were evolving elsewhere, either in Europe, Asia, or North America, and preparing for the great interchange of life which would occur when Africa should again be connected with the other continents."

The explorations carried on in the Fayûm by Dr. C. W. Andrews resulted in the acquisition of a few specimens of interest, one of which (as mentioned in *The Geological Magazine* for March) served to demonstrate that the supposed genus *Phiomia* is really based on a portion of the lower jaw of a young individual of a species of the proboscidean genus *Palæomastodon* retaining the milk-teeth. Very curious is the discovery of the existence of a huge globe-like chamber on the side of the lower jaw of *Geniohyus*, which in life may have contained a gland. There are certain indications that this genus, which was originally regarded as one of the Suidæ, may be related to the hyraxes—an interpretation which would accord best with Prof. Osborn's view. The existence in the Fayum Eocene of remains of a large bird related to the herons is a discovery of considerable interest.

Egypt is, however, by no means the only part of Africa from which discoveries of fossil vertebrates have been recorded during the period under review; and from the fact that mammalian remains have been described from three distinct localities at the opposite extremity of that continent, we may expect in the future to obtain further important information with regard to the past history of the South African fauna. The first of the papers referred to is published in the final report of a recent geological survey of Natal and Zululand, in which Dr. W. B. Scott, of Princeton, New Jersey, gives a description of the two last lower molars of an extinct elephant obtained, in company with remains of rhinoceros, hippopotamus, and antelopes, from a deposit of late Tertiary age in Zululand. The elephant, for which the author proposes the name *Elephas zulu*, has the constituent plates of its molar teeth more numerous and thinner than those of the existing African species. They are described as being to a great extent intermediate in this respect between the latter and those of the extinct European and Asiatic *E. antiquus*; but according to the figures they seem much nearer the molars of the species last named. It is suggested that *E. zulu* may have been the ancestor of the living *E. africanus*, in which case it would almost be imperative to regard the molars of the

latter as being of a degenerate type. This question requires careful consideration; but, apart from this, the discovery is one of great interest.

The diamond-diggings at Kimberley are the place of origin of the second batch of remains, which have been described by Dr. E. Fraas of Stuttgart in the *Zeits. deutsch. Geol. Ges.* for 1907 (pp. 232–43). The specimens include an imperfect mastodon tooth, probably belonging to the same species as the one described last year from Barkley West; and likewise other teeth referable to a zebra, a hartebeest or blesbok, and a hippopotamus. In most instances no attempt is made at specific determination, but the author refers the hippopotamus remains to a large race of the common African species.

The third discovery, reported by Messrs. F. Mendell and E. C. Chubb in *The Geological Magazine* (pp. 443–8), relates to Rhodesia, where remains of existing African mammals have been found associated with stone implements of a palæolithic type.

Passing on to a survey of papers devoted more or less exclusively to particular groups of mammals, brief reference must suffice to one by Dr. F. Ameghino of Buenos Aires in which the author claims man to be of South American origin, his ultimate ancestor being the Tertiary opossum-like genus *Microbiotherium*. Such a phylogeny is not likely to be accepted by naturalists. This paper was published at La Plata.

In March Mr. H. F. Standing read a paper before the Zoological Society of London on extinct Malagasy lemurs, in which he discussed their relations to living lemurs and the higher Primates. The remains were obtained in the muddy bed of a swamp formed by the blocking-up of the River Mazy by a lava-flow, at from a few inches to three or four feet below the surface. They consisted of a large number of skulls and limb-bones of lemurs and lemur-like animals. This material enabled the author to corroborate the view, previously put forward by Dr. Forsyth Major, that the extinct lemurs of Madagascar were, in many respects, intermediate between existing lemurs and monkeys, and to express his belief that New World monkeys and the Lemuridæ, as well as the Malagasy Indrisinæ, had a common origin. He also stated his opinion that, in view of recent additions to our knowledge of lemuroids, and from the evidence of the new collection as to their close relationship to

apes, it was no longer possible to separate the Primates into the suborders Lemuroidea and Anthropoidea. The full text of this communication was not published at the time when the present article was written.

Practically nothing has been accomplished during the year to add to our scant knowledge of the past history of bats. It is true that Mr. G. E. Mason, in the September issue of *The Annals and Magazine of Natural History*, described the remains of a supposed new fruit-bat from Round Island, near Mauritius. These remains occur in a guano-deposit, and appear to be very recent; and in a note on Mr. Mason's communication published in the October number of the same journal, Dr. Knud Andersen pointed out that they appear to be inseparable from the existing *Pteropus rodricensis*.

On the other hand, some very important evidence has been obtained with regard to the palæontology and past distribution of one group of Insectivora. The golden moles (Chrysochloridæ) form at the present day a group entirely confined to Southern and South-Eastern Africa, whose nearest relatives are apparently the tenrecs of Madagascar. An extinct Patagonian insectivorous mammal (*Necrolestes*) has, however, been regarded as a member of the same group; and, more recently, Dr. W. D. Matthew (*Science*, December 14, 1906, and *Bull. Amer. Mus. Nat. Hist.*, vol. xxiii. art. 9, 1907) has announced the discovery in the Miocene strata of South Dakota of the remains of what he regards as an undoubted golden mole, although referable to an extinct genus (*Arctoryctes*). The author also considers that the North American Tertiary genus *Xenotherium*, previously regarded provisionally as a monotreme, is a member of the same group. If the identifications be trustworthy, the discovery is of much interest from the standpoint of geographical distribution. Although its bearings cannot be fully discussed here, it refutes the idea that the Patagonian *Necrolestes* affords any evidence in favour of a former Antarctic land-connection between Africa and South America.

In the paper on the Lower Miocene fauna of South Dakota referred to above, Dr. Matthew, in addition to describing certain new species, discusses the relationship of the Tertiary Canidæ to their existing representatives. In his opinion the Old World *Cyon* and probably the South American *Speothos* (*Icticyon*) are derived from *Temnocyon* of the John Day Tertiary; the

characters of the skull and skeleton confirming the evidence afforded by the dentition. The more typical South American Canidæ appear, on the other hand, to be the nearest living representatives of the middle Tertiary *Nothocyon* and *Cynodesmus*; *Mesocyon* being slightly off the line in the direction of *Temnocyon*.

The generally accepted classification of fossil Canidæ is, moreover, in the same author's opinion, misleading; more especially the association of the genera *Cephalogale*, *Simocyon*, *Oligobunis*, *Enhydrocyon*, and *Hydrocyon* in the single subfamily Simocyoninæ. The two last-named genera are, for instance, probably not separable, and together with *Philotrox* appear to be related to *Temnocyon*, and so with the modern *Cyon*; while *Oligobunis* is probably referable to the Mustelidæ. Again, *Cephalogale*, which has been regarded as ancestral to the bears, seems rather, judging from dental characters, to be related to the typical members of the family (Caninæ); such aberrant features as it possesses in this respect being to some extent paralleled in *Cynodesmus*.

Here it may be well to quote a very important note on classification generally appended by Dr. Matthew to his observations on extinct dogs. It appears, he writes, "obviously improper to separate two closely allied genera or species because they are destined to give rise in the future to two distinct families, in the opinion of the investigator. So far as classification and nomenclature are based upon the facts of structural resemblance or difference, they are permanent, but the attempt to make families, genera, or species correspond with hypothetical phyla is not only misleading but destructive of any approach to uniformity or permanency of arrangement."

These remarks the present writer may take the opportunity of endorsing. An attempt has been made to introduce such a phylogenetic classification in the case of the early Perissodactyla, and the genera *Hyracotherium* and *Systemodon*, which are obviously near relatives, have been referred to distinct families on account of the presumption that while the one is the ancestral form of the horse tribe, the other has given origin to the tapirs.

Dr. Matthew, as already mentioned, transfers *Oligobunis*, which had been regarded as ancestral to *Speothos*, to the Mustelidæ. The short muzzle lacks the constriction in front of the carnassials distinctive of the early Canidæ, and the other dental features,

especially the presence of a distinct notch between the blades of the lower carnassial, are of a musteline type. Very interesting is a short-jawed musteline described as *Megalictis*, with teeth intermediate between those of *Oligobunis* and the living *Gulo* and *Mellivora*, to which latter it appears nearly related.

Certain new rodents, some referable to the well-known beaver-like genus *Steneofiber*, and others to the allied *Euhapsis*, are also described by Dr. Matthew; but these may be passed over without further notice.

Of more general interest is *Epigaulus*, a new horned rodent from the Miocene of Kansas, described by Mr. J. W. Gidley in the *Proceedings* of the U.S. National Museum (vol. xxxii. p. 627). It is the most specialised member of the Mylagaulidæ yet discovered, with the large nasal horns placed just in front of the orbits. Mr. Gidley concludes that while this extinct group of specialised rodents has some remote affinities to the beavers (Castoridæ) and a nearer relationship to the squirrels (Sciuridæ) it has a greater number of characters in common with the sewellels (Haplodontidæ), and also shows certain resemblances in general proportions to some of the Asiatic mole-rats (Spalacidæ). The latter, however, seem due more to modification of the skeleton for burrowing than to real relationship. In tooth-development the Mylagaulidæ have surpassed in specialisation the other Sciuromorpha, and could not have been ancestral to any of the living forms.

Squirrel-like rodents of the genera *Paramys* and *Sciuravus*, from the Eocene deposits of the Wasatch and Wind Rivers, have been described during the year by Mr. F. B. Loomis (*Amer. Journ. Sci.* for February). Both genera are nearly related; the former, at any rate, exhibiting many squirrel-like characters, and being probably one of the ancestral types of the modern family.

The extermination of the urus, or aurochs—the ancient European wild ox (*Bos taurus primigenius*)—forms the subject of a very interesting paper by Dr. A. Mertens published in the *Abhandlungen und Berichte* of the Magdeburg Museum. The author confirms the opinion that the name aurochs belongs to this animal, although it has been misapplied to the bison. It is likewise certain that in the time of Herberstain (the middle of the sixteenth century) aurochs were living in Poland, and were seen alive by him; and, according to other testimony, a herd of thirty was living in the Jaktorowka (or Wiskitki)

forest of the Masovia district of Poland in the year 1564. By 1599 the number was reduced to twenty-four, while in 1602 only four remained, these being reduced in 1620 to one cow, which appears to have been killed seven years later. A few half-domesticated individuals were, however, living in captivity in 1627. Herberstain's statement that the aurochs was typically black, with a light dorsal streak, is accepted. Other evidence tends, however, to show that there were grey aurochs in Poland, and red ones in Central Germany. This is not the only paper on this subject published during the year, as Dr. M. Auerbach, in the *Verhandlungen der Naturwissenschaftlichen Vereins* of Karlsruhe (vol. xx.) has given descriptions of a number of remains of both the urus and the bison preserved in the museum of that city.

Little appears to have been contributed during the year to our knowledge of the past history of the deer tribe. A considerable collection of antlers of reindeer and elk from the Pleistocene of Olai, Livonia, has, however, been described by Mr. G. Schweder, in the *Korrespondenzblatt naturf. Vereins* of Riga, where it is pointed out that in 1831 the name of *Cervus gallinus* was suggested by Fischer for the fossil elk antlers from this district. If, therefore, the European elk be eventually split up into local races, this name will have to be considered.

In the article on vertebrate palæontology contributed to Science Progress a year ago, reference was made to Dr. Lönnberg's opinion as to the near relationship of the "Irish elk" to the reindeer, and to certain arguments which had been advanced against that view. These arguments have been endorsed and strengthened in a note contributed by Dr. R. F. Scharff to the May number of *The Irish Naturalist.*

If the work on fossil Cervidæ has been small and unimportant, that accomplished in America in connection with the extinct ruminating oreodonts, or merycoidodonts, and fossil swine has been extensive. Some of these merycoidodonts are described in the paper by Mr. Peterson already referred to; but by far the most interesting is one from the Miocene of Nebraska, for which Mr. E. Douglass (*Annals* of the Carnegie Museum, vol. iv. No. 2, 1907) proposes the name of *Pronomotherium.* The skull is characterised by its shortness, the presence of a small pair of horns above the orbits and of a large cavity in advance of the same, as well as by the extraordinary depth of the hind part

of the lower jaw. In the opinion of Mr. Douglass, the owner of this skull was furnished with a proboscis of considerable length. The development of horns is probably a sign that the genus belonged to a decadent, or over-specialised, member of the group. Another member of the same genus is described by the author in the *Bulletin* of the American Museum, vol. xxiii. art. 32. Skulls of a number of other forms of these curious "ruminating hogs" are described in the same two papers, but since they belong to well-known genera, further mention is needless.

The work on the swine group is suggestive of somewhat unnecessary genus-making. In a paper published in the *Memoirs* of the Carnegie Museum (vol. ii., No. 8) Mr. O. A. Peterson described a peccary from the Miocene of Nebraska under the name of *Thinohyus siouxensis*. According, however, to Dr. Matthew, *Thinohyus* is inseparable from the White River genus *Perchœrus*; but instead of referring Peterson's species to that genus, he proposes the new generic name *Desmathyus* for a more or less closely allied animal, and regards "*Thinohyus*" *siouxensis* as a primitive aberrant form transitional from *Perchœrus*. Surely in such a case it would be better to include all three forms in one genus. In these Miocene and Oligocene peccaries there were three pairs of upper incisor teeth, instead of the two of the modern *Dicotyles*; but in some of the Miocene species the outer pair is much reduced in size. These later Miocene forms also agree with modern peccaries in having the tympanic bulla of the skull filled with cancellous bony tissue, whereas in the typical *Perchœrus* it is empty.

The evolution of the horse and the mutual relationships of the different domesticated breeds are subjects which continue to attract the attention of investigators on both sides of the Atlantic. Dr. R. S. Lull has drawn up a useful summary of the main facts connected with the evolution of the horse family, which first appeared in the March number of *The American Journal of Science*, but has been reprinted in pamphlet form as a guide-book to the collection in the Peabody Museum at Yale University. Prof. J. C. Ewart, on the other hand, has devoted his attention to a large series of horse-skulls discovered in the Roman fort at Newstead, near Melrose, and published the results of his investigation in the *Transactions* of the Royal Society of Edinburgh, with a summary in an article in the

April number of *The Quarterly Review*. On the evidence of these skulls Mr. Ewart proposes to recognise three types of domesticated horse, severally distinguished by the degree of inclination of the face to the basal axis of the cranium.

During the year Dr. Ameghino has published in the *Anales* of the Buenos Aires Museum (vol. xvi.) a figure of the skeleton of *Hippidium*, a small extinct South American horse remarkable for the great length of the nasal bones and of the slits by which they are separated from the adjacent elements of the skull. A model of the skeleton from which Dr. Ameghino's figure is taken has been installed in the British Museum (Natural History).

A new rhinoceros from Portugal has been named by Mr. Roman in the paper cited above, and Mr. F. Toula (*Jahrb. Geol. Reichsanstalt*, vol. lxvi.) records a new variety of *Rhinoceros mercki* from Austria.

Brief mention may here be made of another paper by Dr. Ameghino in the serial just quoted, where it is pointed out that the skulls of some of the South American toxodonts are furnished with rudimentary horn-like prominences.

As regards the proboscidean group, reference has already been made to the discovery of an extinct elephant and mastodon in South Africa; and it should be added that Dr. Schlosser, in a paper quoted above, has recorded remains of *Mastodon longirostris* from the upper Tertiary of Spain. To the energy of Miss Dorothea Bate science is indebted for the discovery of remains of a pigmy elephant (*Elephas cretensis*) in the caves of Crete; these having been described and figured by their discoverer in the August issue of the Zoological Society's *Proceedings*. To the exhibition galleries of the American Museum has been added a complete skeleton of the Columbian mammoth, discovered in Indiana in 1903. According to a preliminary description by Prof. H. F. Osborn published in the *Bulletin* of the American Museum (vol. xxiii. p. 255), the mounted skeleton stands 10 ft. 6 in. at the shoulder. The largest known tusk of this species or race of mammoth appears to be one referred to in *Science* for 1907 (vol. xxv. p. 971) by Mr. C. H. Sternberg, of which the exposed portion measured 14 ft. in length, with a basal diameter of 8 in.

Of the few papers on fossil cetaceans which have come under the writer's notice, one by Mr. F. W. True, issued as No. 1694 of the quarto series of publications of the

Smithsonian Institution, is devoted to an imperfect skull obtained in 1847 from the Eocene marl of the Ashley River, South Carolina. In the year of its discovery appeared a brief account of the specimen by Mr. M. Tuomey, who referred it to *Zeuglodon*; and two years later it was named *Z. pygmæus* by Prof. J. Müller. The specimen afterwards came under the notice of Prof. L. Agassiz, who caused a plate to be prepared, with the lettering *Phocodon holmesi*; but for some reason this plate was never issued, and in 1895 Prof. E. D. Cope referred the specimen to a new genus, under the name of *Agorophius pygmæus*. Despite the fact that when first figured the specimen had a single *Squalodon*-like tooth in the maxilla, a suggestion was made that the species might be an ancestral rorqual. In Mr. True's opinion, *Agorophius* is, however, a squalodont, differing in cranial characters from *Squalodon* itself. The European *Squalodon ehrlichii* has a broad rostrum recalling the Carolina genus, and may be a connecting link between *Squalodon* and *Agorophius*. The type specimen of another American Tertiary cetacean—*Anoplonassa forcipata*—has also been redescribed by Mr. True (*Bull. Mus. Zool. Harvard Coll.*, vol. li. p. 97), who regards it as representing a member of the Physeteridæ allied to the modern *Mesoplodon*. The rarity of cetacean remains in the Eocene clay of Barton, Hampshire, fully justifies Dr. C. W. Andreas in describing (*Quart. Journ. Geol. Soc.*, vol. lxiii. p. 124) a vertebra of *Zeuglodon wanklyni*; this being the third known specimen of that species. Of the two earlier ones, the second was incorrectly referred to a rorqual, under the name of *Balæonoptera juddi*. Of greater importance is a memoir by Dr. O. Abel, published in the *Denkschriften* of the Vienna Academy (vol. lxxxvi.), on the rudimentary pelvis of cetaceans. At the conclusion of this memoir the author points out that the development of a caudal fin in cetaceans and sirenians has rendered a functional pelvis superfluous in both groups. Among cetaceans and dugongs the reduction has followed parallel lines, culminating in a retention of portions of the ilium and ischium. On the other hand, the manatis have followed a line of their own, and have retained only the ischium.

The only important work on fossil marsupials which has come under the writer's notice is an attempt by Dr. E. C. Stirling (*Nature*, vol. lxxvi. p. 543) to restore the external

form of *Diprotodon*. As regards general contour, Dr. Stirling has followed the lines of a wombat, although with a certain increase in the relative length of the limbs. Since, however, the teeth and fore part of the skull are of the kangaroo type, with some indications of a greater development of the soft parts of the nasal region, the peculiar puffy and cushion-like muzzle of the kangaroo has been introduced, in a somewhat accentuated degree, into the restoration.

Dr. Broom's recent work on the ancestry of mammals receives mention at the end of the section on reptiles.

Work on fossil birds during the period under review appears, as usual, to have been but small, The discovery of a leg-bone of a heron-like species in the Eocene of Egypt has been already mentioned. Another lower Tertiary bird has been identified by Dr. O. Abel (*Centralblatt für Mineralogie*, 1907, p. 450) in the shape of a large coracoid from the upper Eocene of Choctaw County, Alabama, which had been mistaken for a zeuglodont bone. That this bird, for which the name *Alabamornis gigantea* has been suggested, was of huge size, and therefore flightless, is certain; but whether it was related to *Diatryma* of the North American and *Gastornis* and *Remiornis* of the European Eocene must for the present remain doubtful.

In connection with birds, reference may be made to an exceedingly able and interesting paper on the origin of flight in vertebrates by Baron Francis Nopcsa, published in the June issue of the *Proceedings* of the Zoological Society of London. In the opinion of the author, bats and pterodactyles are the descendants of four-limbed arboreal creatures in which, owing to the development of a flying-membrane (*patagium*), the fore-legs had become to a certain degree adapted for flight, and in consequence less well suited for terrestrial progression. Birds, on the other hand, are regarded as having been evolved from running bipedal dinosaur-like reptiles, in which the front limbs, owing to a flapping movement, became modified into wings, without any concomitant loss of the cursorial power of the hind-limbs. It is on account of this superior mode of development that birds have outstripped both pterodactyles and bats in the contest for the "command of the air." They may be likened to "äeroplanes," whereas their rivals have not passed the "air-ship" stage. Baron Nopcsa's paper is illustrated with a restoration of a cursorial "pröavis."

From the preceding paragraph we are led by an easy transition to pterodactyles, on which group, as represented in the upper Jurassic strata of Swabia, Dr. Felix Plieninger has contributed an important memoir to the Stuttgart *Palæontographica* (vol. liii., Nos. 4–6). Several beautifully preserved skeletons from the Lithographic Stone of Nusplingen and other Swabian localities are figured, for one of which the new name *Rhamphorhynchus kokeni* is proposed. The generic position of the English *Scaphirhynchus purdoni* is also discussed at some length.

Having completed the survey of the extra-European Triassic dinosaurs, Prof. F. von Huene has commenced in *Geologische und Palæontologische Abhandlungen* (Jena, 1907) a detailed description of their European representatives. The first part is devoted to the dinosaurian remains from the Keuper of the Nürenberg district, first brought to notice by Engelhardt in 1834, and afterwards referred to *Thecodontosaurus* and *Palæosaurus* of Riley and Stuchbury, which were long regarded as a general receptacle for Triassic dinosaurs of all descriptions. Dr. von Huene refers all the remains described in this part to von Meyer's genus *Plateosaurus*, of which, in addition to the typical *Pl. engelhardti* and *Pl. queustedti*, he recognises the new species *Pl. reinigeri* and *Pl. erlenbergiensis*.

A redescription of the type skeleton of the sauropod dinosaur *Morosaurus agilis* forms the subject of a paper by Mr. C. W. Gilmore in the *Proceedings* of the U.S. National Museum (vol. xxxii. p. 151), in which it is suggested, on account of the primitive character of the vertebral column, that this species may belong to the genus *Hoplocanthosaurus*. To the sauropod genus *Pelorosaurus*, typified by a humerus from the English Wealden, Mr. H. E. Sauvage (*Bull. Soc. Boulogne-sur-mer*, vol. vii.) refers part of a femur from the Jurassic of the Boulonnais; also mentioning that the teeth from the same deposit described as *Neosodon* and *Caulodon* likewise pertain to the same genus.

Dinosaurian remains from the Jurassic and (?) Cretaceous of Madagascar have been described by Mr. A. Thevenin in the *Annales de Paléontologie*, vol. ii. pt. 3. Some of these are referred to *Bothriospondylus madagascariensis*, a species described several years ago by the present writer; while others are assigned to *Titanosaurus* and *Megalosaurus*. As *Titanosaurus* is typically

from the Cretaceous of Central India, its reappearance in Madagascar has an important bearing on the theory of a former land-connection between those two countries.

Great interest also attaches to a couple of skeletons of a small reptile from the Trias of Lossiemouth, Elginshire, regarded by Dr. H. Smith Woodward (*Quart. Journ. Geol. Soc.*, vol. lxiii. p. 140) as representing a new type of dinosaur, for which the name *Scleromochlus taylori* is proposed. The pelvis is unlike that of the Rhynchocephalia, while the absence of bony armour and the apparent perforation of the acetabular cavity of the pelvis distinguish the skeleton from the Parasuchia. On the other hand, the observable characteristics seem distinctly dinosaurian, and appear to indicate relationship with the Triassic American genera *Ammosaurus*, *Anchisaurus*, and *Hallopus*. The large skull, apparently toothless jaws, and the firm union of four elongated metatarsal bones are, however, peculiarities of the Elgin reptile, which was evidently a specialised type. The extreme lightness of the skeleton, coupled with the elongation of the hind-limbs, suggests leaping habits.

Passing on to the Parasuchia, or Phytosauria, we find that in America Mr. J. H. Lees has described in *The Journal of Geology* (vol. xv. p. 121) a new genus and species from the Trias of Wyoming, under the name of *Palæorhinus bransoni*. The genus is akin to the American *Rhytidodon*, from which it appears to be mainly distinguished by a difference in the form of the ilium. In Europe Prof. E. Fraas (*Jahreshefte Ver. Naturkunde Württemberg*, 1907, p. 101) has made known a new species of *Aëtosaurus* from the upper Stubensandstein of Stromberg, near Pfaffenhofen, under the name of *A. cristicauda*. In regard to the group to which these reptiles belong, it is remarked that one of the most important differences from the typical Parasuchia is the smaller share taken by the ischium and pubis in the formation of the acetabulum. This and other differences do not, however, necessitate ordinal separation from that group, of which the Aëtosauria may be regarded as a specialised branch, distinguished by the peculiar type of the dermal armour.

The acquisition by the Belgian Museum of a number of vertebrate remains from the Eocene strata of Erquelinnes, near Hainault, has enabled Dr. L. Dollo (*Bull. Soc. Belge Géol.*, vol. xxi. p. 3) to describe a new type of crocodile, to which he has given the name *Eosuchus lerichei*. Although a member

of the modern group of the order, this genus, in the less backward position of the posterior nostrils, makes some approximation to Jurassic forms.

A memoir on the structure and adaptive modifications of the armourless marine Jurassic crocodiles of the genus *Metriorhynchus*, by Mr. G. von Arthauber (*Beitr. Pal. Ost.-Ung.*, vol. xix. p. 287, 1906) has given rise to a considerable amount of discussion. In the *Centralblatt für Mineralogie* (1907, p. 225) Dr. O. Abel criticised the memoir somewhat severely, and published an amended restoration of the external form of *M. jækeli*, in which the reptile is represented with flipper-like limbs and a double-lobed tail-fin. Later on in the same volume (p. 353) further criticisms are published by Mr. E. Auer. To all these Mr. von Arthauber replied in the *Centralblatt* (p. 385), where his own views are maintained; while in a second paper he gave further details with regard to the structure of the skeleton of the hind-limb, directing special attention to the arrangement of the tarsal bones. Another contribution to the osteology of the genus, as represented by *M. superciliosus* of the English Oxfordian, has been made by Mr. E. T. Leeds in *The Geological Magazine* (decade 5, vol. iv. p. 314), where attention is directed to the confusion which has arisen owing to a portion of the coracoid having been wrongly described as the scapula.

Among more typical crocodiles, Mr. R. W. Hooley (*Quart. Journ. Geol. Soc.*, vol. lxiii. p. 50) has described a fine skull and other remains of *Goniopholis crassidens*, obtained after the fall of the cliff of Wealden strata at Atherfield, Isle of Wight. The identification by Dr. A. S. Woodward (*l.c.*, p. 132) of the same genus, in the form of *G. Hartti*, in the Cretaceous rocks of Bahia, Brazil, is of considerable interest.

In the only paper on fossil snakes which has come under the writer's notice, Dr. W. Janensch (*Archiv. für Biontologie*, vol. i. p. 313) discusses the monster serpent *Pterosphenus schweinfurthi*, of the Fayum Eocene, and supports the view that it is rightly associated with the European *Palæophis* in a separate family, the Palæophidæ, which is more nearly related to the pythons than to the sea-snakes, despite the fact that its representatives were marine.

Important information with regard to the osteology of the ichthyosaurs has been furnished by Dr. C. W. Andrews in a paper on the Oxfordian *Opthalmosaurus leedsi* published in the May number of *The Geological Magazine*. This species is

remarkable for the great variation exhibited by the bones of different individuals, this feature apparently indicating that these reptiles were in a state of developmental inæquilibrium. A restoration of the back of the skull has been attempted, which shows that the whole arrangement is adapted to give the greatest possible rigidity to the quadrate—doubtless for the purpose of affording a firm support for the long jaws. The stapes, which, according to the author, has lost its function as a bone of the internal ear, is firmly united at one end with the basi-occipital, whilst its other extremity is fitted into a pit-like facet of the quadrate.

This conclusion as to the stapes (or columella) having no connection with the auditory function is disputed by Dr. Louis Dollo in a note published in the *Bulletin de la Société Belge de Géologie*, vol. xxi. p. 157, who suggests that it has a kind of secondary auditory function, connected with the diving or "sounding" habits of the ichthyosaurs. Such a function he considers to be connected with a modification of the cerebral circulation and paralleled by the conditions obtaining in cetaceans.

The description by Mr. C. W. Gilmore, in the March number of *The American Journal of Science* (vol. xxiii. p. 193), of a new species of *Baptanodon* from the Jurassic of Wyoming is of interest from the fact that the remains are less incomplete than those of any other known specimen of the genus.

On account of the excessive width of the front paddle, which comprises eight longitudinal rows of bones, the skeleton of a new species of ichthyosaur (*Ichthyosaurus platydactylus*) from the Chalk of Kastendamm, Hanover, described by Mr. F. Broili in vol. liv. of the Stuttgart *Palæontographica*, is of more than ordinary interest. At the close of his memoir the author illustrates diagrammatically the fact that in the Liassic ichthyosaurs the front paddles and tail-fin are relatively much larger than in the Cretaceous species, this apparent loss in the latter of propelling power being compensated by an increase in the width of the fore-paddles.

Considerable importance attaches to an account of the Cretaceous pliosaurian genus *Brachauchenius* given by Mr. S. W. Williston in No. 1540 (vol. xxxii. p. 477) of the *Proceedings* of the United States National Museum. *Brachauchenius*, which is known from West Kansas, is regarded by its describer as closely related to *Pliosaurus*, from which it differs in having single-

headed cervical ribs. From other plesiosaurians in which the skull is fully known, it differs in that the palatines meet each other in the middle line, but this is a feature which the author thinks will be met with in *Pliosaurus*. The assumed relationship of the plesiosaurs to chelonians is disputed. The latter lack, for instance, epiphyses to the humerus, while such resemblance as exists between the shoulder-girdle in the two groups is due to adaptation. Chelonians are without the parietal foramen of plesiosaurs, and retain the hypocentral mode of articulation of the ribs, whereas in plesiosaurs the ribs are attached to the transverse processes of the vertebræ. Sauropterygia are, indeed, probably descended from theriodont ancestors, while Chelonia appear to be derived from a cotylosaurian type, both being widely sundered from ichthyosaurs and rhynchocephalians.

Brief reference will suffice to a paper by Mr. F. Broili, published in the *Centralblatt für Mineralogie*, on certain reptilian remains from the Kössen beds of the Trias of the Alps. From the form of the dorsal vertebræ and the stoutness of the abdominal ribs, the specimens evidently indicate one of the nothosaurs, or primitive sauropterygians. Their large size suggests affinity with *Partanosaurus*, but in structure the vertebræ appear to display characters intermediate between those of that genus and those of *Nothosaurus*.

In a communication to *Science* for 1906 (vol. xxiv. p. 184) Prof H. F. Osborn states that the American Museum has received from the Brazilian Coal Commission natural casts of a small Permian reptile near akin to *Stereosternum* of the same country and horizon, and to *Mesosaurus* of the South African Permian. An opinion is quoted to the effect that none of these reptiles are related to the plesiosaurs (Sauropterygia).

The huge Eocene turtle known as *Eosphargis gigas*, typically from the London Clay, also occurs in the corresponding formation of Belgium, where an almost complete specimen has been discovered at Quenast. According to Mr. Dollo (in the serial already quoted) the upper shell, or carapace, of this turtle is quite different from that of the modern leathery turtle, and is of the general type obtaining in ordinary turtles.

Remains of soft river tortoises (Trionychidæ) from various North American horizons form the subject of a paper by Mr. O. P. Hay in the *Bulletin* of the American Museum, vol. xxiii. art. 34.

The list of rhynchocephalian reptiles has been increased by Dr. R. Broom's description (*Trans. S. African Phil. Soc.*, vol. xvi. p. 379) of the new genus *Palacrodon browni*, from the Triassic division of the Karoo series of South Africa. Dr. Broom, it may be added, restricts the Rhynchocephalia to reptiles with a radiating pelvis, and therefore excludes the Indo-European Triassic genera *Palæohatteria*, *Rhynchosaurus*, and *Hyperodapedon*, in which the pelvis is plate-like. On this view, *Palacrodon* is the only Triassic representative of the order.

During the year important work has been accomplished in that remarkable group of Permian reptiles known as the Pelycosauria. In an article published in the *Bulletin* of the American Museum (vol. xxiii. p. 265), Prof. H. F. Osborn has given a figure of the skeleton of the Texan "ship-lizard," *Naosaurus claviger*, with an attempted restoration of the creature's bodily form. The length of the skeleton is 6½ ft. Among the more striking features are the enormous head, armed with powerful teeth, and the great height of the spines of the vertebræ of the long back, which are furnished with transverse bars recalling yard-arms, and thus suggesting the name of the genus. The restoration of the allied genus *Dimetrodon* has been essayed by Dr. E. C. Case in vol. xv. of *The Journal of Geology*.

Of far more importance is the monographic revision of the Pelycosauria by the last-named naturalist, published by the Carnegie Institution of Washington. After discussing the various opinions as to the proper systematic position of these reptiles, the author concludes that they really form a subordinal group of the Rhynchocephalia. They all had notochordal vertebræ, with intercentra, and two-headed ribs; but it was only in the more specialised forms that the spines of the vertebræ attained the characteristic development. All were carnivorous. The more primitive representatives of the group, constituting the new family Poliosauridæ, are not far removed from the Permian rhynchocephalians of the suborder Protorosauria; but the other forms display great specialisation, which to a great extent obscures their rhynchocephalian affinities. The great development of the dorsal spines of the vertebræ is the most obvious feature of this specialisation, but it is accompanied by others such as the roofing over of the upper temporal fossa, the mode of rib-attachment, and the enormous size of the claws. Although in earlier stages the spines may have served some useful purpose,

in their full development they are regarded by Dr. Case as a mere redundancy of growth, possibly an example of that development of spiny outgrowths and excrescences which appears to mark a decadent group. In addition to North America, pelycosaurs occur in Bohemia (*Naosaurus*), and not improbably in Central Germany and France; but they appear to be unknown in Russia and Africa.

Coming to the anomodont, or theromorphous, group, we find Dr. R. Broom, in the journal already quoted (p. 376), describing a new species of the theriodont genus *Ælurosaurus* from Aliwal North; while in the *Annals* of the Natal Museum (vol. i. p. 168) he makes known a new *Dicynodon* and a new *Scymnosaurus* from that colony. *Scymnosaurus*, which is one of the carnivorous types, appears to be nearly related to *Inostranzevia*, of the Russian Permian. In America, Dr. Case has recently described two nearly complete skulls of the cotylosaurian genus *Bolosaurus*, from the Permian of Texas; the paper forming article 28 of vol. xxxii. of the *Bulletin* of the American Museum.

The relationship of the anomodonts (in the widest sense of that term) to mammals has continued to attract the earnest attention of Dr. Broom, who, in a paper published in the *British and South African Association's Report* for 1907 (vol. iii. p. 12), summarises the evidence in the following words:

"We may regard it as fairly well established that mammals are descended from one of the mammal-like reptiles, and almost certainly from a cynodont (theriodont). The known cynodonts are mostly too large to have been the ancestors, but there is evidence of there having been numbers of small forms, and it was probably from one of these that the new stock arose. And I think we may also safely conclude that all mammals are descended from one common ancestor. By one or two authorities it has been argued that the monotremes are a race apart, and it has even been suggested to remove them from the mammals altogether; but all recent research has confirmed the earlier view that monotremes are typical mammals, and in skeletogenesis are quite as near the marsupials as the marsupials are to the higher forms."

It may be added that Dr. Broom is firmly convinced that *Tritylodon* is a mammal. "As it can be shown," he writes, "from the structure of the molars, that the lower jaw was moved backwards and forwards, as in rodents, it is impossible

that the articulation can have been of the theriodont type, and we must conclude that Owen's opinion was correct that *Tritylodon* was a mammal."

The following interesting case of apparent affinity between anomodonts and mammals given by Dr. Broom in the *Zool. Anzeiger* (vol. xxviii. p. 106) may likewise be quoted. It has long been known that in the human subject, and apparently in mammals generally, there exists a remarkable peculiarity in the development of the metacarpal bones of the hand and the metatarsals (or corresponding elements) of the foot. In the metacarpal (or first joint) of the thumb and the metatarsal of the great toe the separate cap, or epiphysis, is situated at the basal extremity, whereas in the other metacarpals and metatarsals it is developed at the opposite end of the bone. The solution of the puzzle has been found by Dr. Broom, who has discovered that in anomodonts the outermost of the second row of bones in the wrist and the ankle is so elongated as almost to resemble a metacarpal or metatarsal. Owing to this elongation, the main joint of the thumb and great toe appears to have been between the wrist or ankle and the metacarpal or metatarsal (as the case may be), while in the other digits this joint was situated between the metacarpal or metatarsal and the first segment of the fingers or toes. Those ends of the bones which took part in the main joint would be the last to ossify, and would determine the points where the caps, or epiphyses, would form. The anomaly in this respect in the human subject seems therefore to be a direct inheritance from reptilian ancestors.

Work on labyrinthodonts (stegcephalians) appears to have been limited. Prof. H. G. Seeley has, however, described in the October number of *The Geological Magazine* a new genus and species from the Karoo series of South Africa under the name of *Ptychosphenodon browni*; and Mr. E. C. Case (*Bull. Amer. Mus. Nat. Hist.*, vol. xxiii. p. 665) has published notes on remains from the Permian of Texas which throw additional light on the structure of the genus *Zatrachys*.

Perhaps the most important contribution to fossil ichthyology is a memoir by Mr. C. R. Eastman on the Devonian fishes of the New York district, published by the New York State Museum. The memoir, in addition to a large mass of descriptive and technical detail, is written from a broad and philosophical

standpoint, and contains much information and many suggestions as to the habits, phylogeny, and migrations of these Palæozoic fishes. An interesting generalisation, based upon examples from numerous groups, is that those types of fishes which show no tendency to progressive evolution undergo a kind of degenerative development so as to assume a more or less distinctly eel-like form of body. This is true among the acanthodian sharks, which declined towards the close of the Palæozoic epoch, dying out with the Permian. Their fins, being essentially skin-structures, were incapable of strengthening by bony rods, after the fashion obtaining in other contemporary and competing groups. Hence these fishes, as they became worsted in the struggle for existence, changed their habits and their physical structure. Devonian species, for example, with the graceful fusiform proportions of swift swimmers, became replaced in the Carboniferous by overgrown, unwieldy creatures like *Gyracanthodes*, which were evidently grovellers in the slimy mud of land-locked seas and estuaries; while the expiring Permian forms exhibit a distinct approximation to the eel-like type of body.

Passing southward of the isthmus of Panama, fish-remains from the Cretaceous of Bahia form the subject of a paper by Dr. A. Smith Woodward in *The Quarterly Journal of the Geological Society* (vol. lxiii. p. 131). These indicate a curious mixture of Wealden and middle or upper Cretaceous types; *Lepidotus mawsoni* being, for instance, near akin to the well-known *L. mantelli* of the English Wealden, while *Megalurus mawsoni* appears to be a Jurassic rather than a Cretaceous form of amioid fish. On the other hand, the freshwater herring *Diplomystus longicostatus* is a member of a genus common in the upper Cretaceous of the Lebanon and the lower Tertiaries of Europe and North America. The new genus and species *Mawsonia gigas*, a member of the cœlacanth ganoids, may be either Jurassic or Cretaceous, although more probably the latter.

The same author has contributed to *The Geological Magazine* (decade 5, vol. iv. p. 193) an account of the fossil fish-fauna of Pernambuco, in which the new species *Rhinoptera prisca* is described.

From the Lahontan beds of Nevada have been obtained remains of a stickleback, which is regarded by Mr. O. P. Hay

(*Proc. U.S. Nat. Mus.*, vol. xxxii. p. 271) as a subspecies of the existing freshwater *Gasterosteus williamsoni*, whose range extends from Alaska to California. The interest of the identification lies in the inference that the Lahontan beds are not older than the Pleistocene.

Pycnodont fishes from the Cretaceous of the Lebanon form the subject of a paper by Mr. E. Henmy in the *Centralblatt für Mineralogie* (1907, p. 360); while Mr. Erich Heineke has published in vol. viii. pt. 3 of *Geol. und Pal. Abhandlungen* a detailed account of the ganoids and teleosteans of the Lithographic Limestone of Nusplingen.

Of *Amyzon brevipinne*, a fish hitherto known only by a single specimen from the (probably Oligocene) Amyzon beds of British Columbia, Mr. L. M. Lambe has described, in the *Transactions* of the Royal Society of Canada (vol. xii. p. 151), a second and less incomplete example from the same horizon. The palæoniscid *Myriolepis hibernica*, from the Irish Coal Measures, forms the subject of a note in the *Annals and Magazine of Natural History* for December 1906 (ser. 7, vol. xviii. p. 416).

In the elasmobranch group Prof. E. Fraas (*Neues Jahrb, Mineral.*, 1907, vol. i. p. 1) gives further details of the structure of the rostrum and dentition of *Propristis schweinfurthi*, a sawfish from the Egyptian upper Eocene. In this fish the "saw," which is slender and abruptly truncated at the tip, and attained a length of rather more than two metres, has the same internal structure as in *Pristis*, but carries teeth only in its terminal fourth; these teeth being short and broad-crowned, with sharp fore-and-aft edges, which slightly overlap one another, thus forming a sawing implement of great power and efficiency. Of the well-known selachian genus *Hybodus*, Prof. E. Koken gives further structural details in a memoir of considerable morphological importance published in *Geol. und Pal. Abhandlungen*, vol. ix. pt. 4.

The controversy as to the mutual relationships and general affinities of the more primitive Palæozoic fishes and fish-like creatures is maintained with unabated vigour in several papers by Dr. O. Jaekel and Dr. L. Dollo. The first group of these papers, most of which were published in 1906 (although they were not noticed in the article on the present subject in last year's SCIENCE PROGRESS), deal with the imperfectly known

ptyctodonts, as represented by the genera *Ptyctodus*, *Rhynchodus*, *Palæomylus*, and *Rhamphodus*. In the British Museum *Catalogue of Fossil Fishes* the group, of which only three genera were then known, is placed in the chimæroid order of the Holocephali. In a paper on Devonian fishes published in *Sitz.-Ber. Ges. nat. Freunde, Berlin*, for 1906 (p. 77) Dr. Jaekel accepted this arrangement, with certain modifications. Somewhat later Dr. Dollo (*Bull. Soc. Belge Géol.*, vol. xx. p. 133) denied that the ptyctodonts were Holocephali, although not giving his full reasons for the statement. This was in June, 1906, and a month later Dr. Jaekel (*op. cit.*, p. 180) changed his previous opinion, and classed these fishes in the sturgeon group (Chondrostei). During the present year Dr. Dollo has published a paper (*op. cit.*, vol. xxi. p. 1) in which he not only maintains the opinion that the ptyctodonts cannot be classed with the chimæroids, but goes a step further, and definitely places them in the Arthrodira, that is to say with *Coccosteus* and its relatives. He also expresses his opinion that the Holocephali are specialised derivatives from the Palæozoic cochliodont sharks.

In another paper, on the new genus *Pholidosteus* and the mouth-opening and bodily form of the Placodermata, published in the *Sitz.-Ber. Ges. nat. Freunde, Berlin*, 1907 (p. 170), Dr. Jaekel reiterates the views expressed by him in 1902 in regard to this group. Our readers may be reminded that under the title of "Placodermata" the author unites the Ostracodermata (*Pteraspis*, etc.) with the Arthrodira (*Coccosteus*, etc.), although by most authorities the two latter are widely separated. Dr. Jaekel regards all the placoderms as true fishes, which, apart from the retention of certain ancestral features derived from amphibians, are related to the Holocephali (chimæroids), Elasmognathi (sharks and rays), and Chondrostei (sturgeons), with some indications of kinship to the Dipnoi (lung-fishes). These groups he would brigade together under the title of Hypostomata, in contradistinction to the Teleostomata, which include all other fishes.

The list of these primitive fishes has been augmented by Mr. E. Hennig's description, in the *Centralblatt für Mineralogie*, 1907, p. 584, of a new species from the Palæozoic rocks of Gerolstein, referred to the genus *Macropetalichthys* (an ally of *Asterolepis*), with the name *M. pelmensis*.

THE TRANSFORMATIONS OF ELEMENTS

PART I.—THOSE DETECTED BY RADIOACTIVE METHODS; WITH SOME ACCOUNT OF THE PROPERTIES OF THESE ELEMENTS, SO FAR AS KNOWN

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Section 1.—Methods employed in the Detection of Radioactivity: Thorium and its Products

Radioactive substances are defined as those which possess the property of *spontaneously* emitting *radiations* or *rays* capable of passing through plates of metal, or other substances opaque to light. The word *ray* was first used in a definite sense by Newton, who employed it both in the sense of undulations and of corpuscles, in the latter sense especially in defending the old corpuscular theory of light. The rays, or radiations, emitted from radioactive bodies may be in like manner either corpuscular, or consist of undulations in the ether; both kinds are known. Such radiations possess certain characteristic properties. The most important are their penetrative power, emphasised in the definition, their action on photographic plates, and especially their property of discharging electrified bodies. The second of these properties first led to their detection; the last is the means most commonly employed in their study.

Cathode rays and *Röntgen* or *X-rays* possess such properties. So do the rays emitted under certain conditions by zinc sulphide and similar substances. They are not produced

spontaneously, however; the substances producing them are not radioactive.

In 1896 Henri Becquerel found that potassium uranyl sulphate emitted rays which acted on a photographic plate enveloped in black paper, and even separated from the uranium salt by thin plates of metal and other opaque substances. He found later that all the compounds of uranium, and the metal itself, possessed the same property. They not only appeared capable of giving off these radiations continuously, thereby giving rise to a continual supply of energy, but seemed perfectly unchanged by so doing. The action is spontaneous, and uranium is therefore the first element in which the property of radioactivity was discovered.

Uranium salts, besides acting on photographic plates, possess the other radioactive property of discharging electrified bodies. A charged *electroscope* consisting of strips of gold or aluminium leaf suspended from an insulated support, and separated from each other by the repulsion of their electric charge, is usually employed to test materials supposed to be radioactive. Not only is the electricity discharged by radioactive materials, but the rate at which the leaves fall together varies with the degree of radioactivity, other conditions being the same. Different uranium salts discharge an electroscope at different rates; they have different *activities*. Madame Curie has shown that this difference is due, primarily, to the varying proportion of uranium; the radioactivity is proportional to the percentage of uranium in the salt employed. When she extended these quantitative measurements to uranium minerals, this relationship was found to hold no longer. Certain varieties of pitchblende—which consists largely of uranium oxide—were four times as radioactive as the uranium they contained. Chalcolite, copper uranium phosphate, was twice as active; artificial chalcolite gave a figure agreeing with theory. These differences led M. and Mme. Curie to analyse systematically the mineral pitchblende, using the degree of activity as a test for every precipitate, and separating by repeated operations the radioactive from the inactive precipitates. In this way the two elements *polonium* and *radium* were isolated in 1898.

By similar methods during the last eleven years no fewer than twenty-four new elements have been discovered, most of

them radioactive. The history of science shows no parallel with the advance made in this subject. It is comparable with half a century's work in other directions of research. The advance is due in great part to the work of Prof. Ernest Rutherford, who has co-ordinated the facts by putting forward, and in part proving, the first reasonable theory to explain the great mass of data which is even yet accumulating.

The electrical measurements of radioactivity are made with some form of electroscope or electrometer. The electroscope devised by C. T. R. Wilson, and used largely for measuring

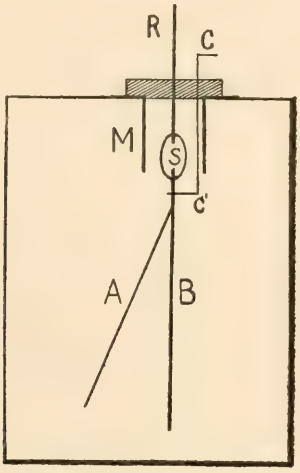

FIG. 1.

small amounts of activity, may be taken as typical. The description is that in Rutherford's *Radioactivity*, p. 86. A brass cylindrical vessel (or very frequently a tin can) is stoppered at the metal mouthpiece M (fig. 1) by an ebonite cork or an ordinary cork covered with sulphur. Through this passes a metal rod R, supporting a sulphur bead S, which supports and at the same time insulates a narrow brass plate B some two or three inches in length. To the upper end of the brass plate is attached a strip of gold, or better, aluminium, A. The sliding metal rod CC′ is used to charge the leaf system, usually by touching it with a charged rod of sealing-wax while it is in contact with B. R is earth-connected and C revolved to break the

contact with the brass and aluminium. The charged aluminium leaf is repelled through a considerable angle. Its movement is observed by a telescope through windows in the brass or tin vessel. The telescope carries a scale; observations are made of the time taken by the falling leaf to traverse a certain fixed portion of that scale. The bottom of the vessel is usually removable, the substances to be tested for radioactivity being thus introduced. In testing gases an airtight apparatus is used and the gases are introduced through metal stopcocks.

Under ordinary conditions, in the absence of radioactive matter the time taken by the falling leaf to pass over the fixed portion of the scale is termed the *natural leak* of the electroscope. This natural leak is quite considerable, and the time may even amount to several hours. The presence inside the case of a comparatively weak radioactive substance reduces the leak to a few minutes, or even seconds. It is desirable to give some account of the reasons underlying this behaviour.

An electroscope can be discharged readily through the action of several different kinds of energy. Thus rays of ultraviolet light allowed to fall on the outer disc of an ordinary electroscope, or the rays given out by a lighted candle placed near it, cause the leaves to fall together rapidly. X-rays behave similarly, and through a detailed study of their behaviour J. J. Thomson and Rutherford have put forward a theory capable of explaining the whole series of phenomena; so far it has stood the test of experience. The different rays are supposed to give rise to particles termed *ions* carrying either positive or negative charges of electricity. The initial action is a collision with an atom of the gas which the ray is traversing; an *electron*, or negative particle of electricity, is set free, the atom minus this electron exhibiting a positive charge. Both, by virtue of their charges, attract to themselves a cluster of uncharged atoms. The number in the case of the electron is estimated at about thirty; the positive cluster is smaller. Both clusters behave like ordinary charged bodies, being attracted by unlike, repelled by like, charges of electricity. Consequently in the absence of any strong electric charge in their neighbourhood they ultimately collide with each other, and their charges become neutralised. But if such ions are liberated in the neighbourhood of a charged

electroscope, it will attract ions with unlike charge in sufficient number to discharge itself (since the charge on the electroscope is likewise due to the presence of free electrons, if negative, or to free positive ions).

It is found that ordinary air always contains a certain very small number of ions, and the natural leak of an electroscope is due to their presence. Again, the production of ions is strictly proportional to the number of rays—*e.g.* if two quantities of uranium oxide are taken, one twice the weight of the other, and they are spread out in thin films of the same thickness, so that the first has twice the exposed area of the second, it will emit twice as many rays as the second; they will produce twice the number of ions, having twice the effect on the leaves of an electroscope; hence it will be discharged in half the time. Similarly if equal quantities of two radioactive materials are taken, and consecutively introduced inside an electroscope, and it is found that the rate of discharge of the first is twice as fast as that of the second, then it is said to possess twice the activity of the second. The measure of the discharge-time gives a measure of the radioactivity. By comparing the effect produced by a substance from day to day, a measure of the variation in its radioactivity is obtained.

The most convenient instrument for these measurements, however, is some form of quadrant *electrometer*, preferably the modification invented by Dolezalek in 1901. This has a very light needle of silvered paper, carrying a small mirror, and suspended by a very fine quartz fibre between the four quadrants. One pair is connected to earth, the other to an insulated metallic plate, facing a second which carries the radioactive matter to be tested. Through action similar to that in the case of an electroscope an electric stress is set up between the two pairs. The needle, previously charged to a very high potential, is repelled from one pair of electrodes towards the other; on account of its extreme lightness it moves at a uniform rate. The time taken to pass two fixed points is observed by means of a stop-watch. As in the case of an electroscope, this time is inversely proportional, other conditions being the same, to the degree of radioactivity of the deposit under observation. The natural leak of the electrometer is deducted from all other time measurements. The electrometer is standardised from time to time against a definite amount of uranium oxide, which is known

to give a constant supply of radiation. In this way any variations in the instrument are corrected.

The photographic action of the radiations has been largely used in certain branches of the subject, but does not give good quantitative results. The method employed is the exposure of the photographic plate wrapped in black paper—to cut off phosphorescent light—to the effect of the radiations. The time of exposure varies from a few minutes, with almost pure radium preparations, to perhaps seventy-two hours, with very weak radioactive preparations. With long exposures the results are especially untrustworthy on account of the difficulties experienced through the plates fogging.

In order to show how the instruments are actually employed and deductions made, a brief account will be given of the results obtained to the present time from the study of **thorium** compounds. The greater part is taken from Rutherford's *Radioactivity*, second edition.

Schmidt and Madame Curie independently discovered the radioactivity of thorium compounds in 1898. Four years later Rutherford and Soddy found that the thorium hydroxide precipitated by ammonia from a solution of the nitrate was less than half as active as the original solid salt; the filtrate on evaporation gave a residue which, weight for weight, was several thousand times more active. They named this active residue **thorium** X (ex-thorio). It consisted largely of impurities existing in the original nitrate; the true thorium X was present only in minute quantity, and could not be separated. It became inactive at the end of a month; in the same time the thorium completely regained its activity. They concluded therefore that thorium X was actually produced from thorium. They proceeded to study the time-rates of these processes, making electrical measurements at intervals over a long time. Their results are shown in fig. 2, A (*Radioactivity*, p. 221); the curves are typical of most of those illustrating the decay and production of radioactive matter. The initial activity of thorium X was arbitrarily taken as 100; similarly that figure was taken for the final activity of the thorium compound. The activities were expressed along the ordinates, the times from the initial measurement along the abscissæ. The initial irregularities in the curves were due to the presence in the original thorium compound of further

disintegration products of thorium X; these are also radioactive, and produce their own electrical effect. They were precipitated with the thorium hydroxide. The initial part of the *recovery curve* is due to their activity rapidly becoming smaller as they themselves disintegrate—more rapidly than is counteracted by the gradual reproduction of thorium X. The initial part of the *decay curve* is due to their reproduction from thorium X, when their activity gives an added effect to the activity of thorium X itself. In both cases a time is reached when in any given interval, say a minute, as much of these substances is produced as decays in that same time. These

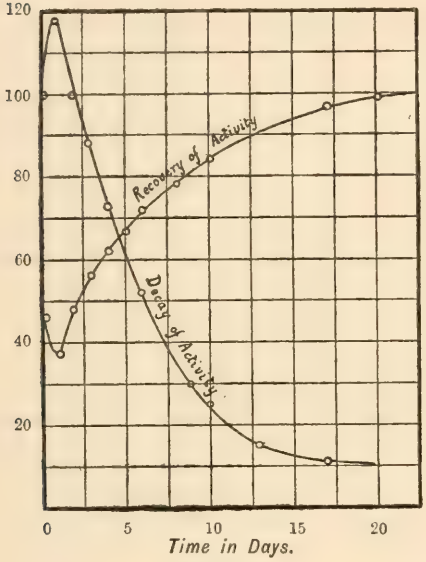

FIG. 2 A.

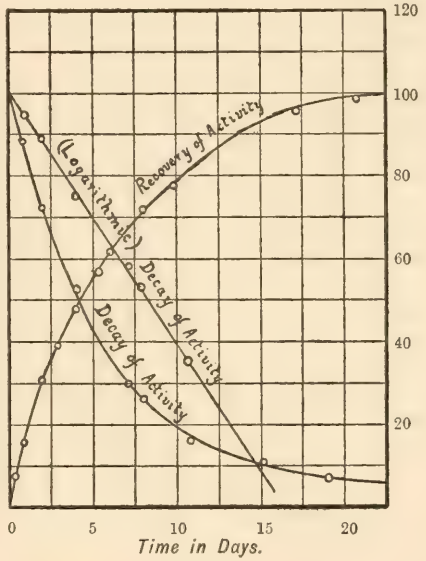

FIG. 2 B.

products are then said to be in *radioactive equilibrium*, and no longer affect the nature of the curve. The times in question are represented by the minimum and maximum on the respective curves, and it will be noticed that these exactly correspond. If the true curves are then continued back till they meet the axis, and the maximum values in both cases again taken as 100, the corrected values are shown in fig. 2, B (*Radioactivity*, p. 222). The decay curve is *logarithmic*, that is to say, if the logarithms of the activity values are plotted against time (instead of the true activity values), the result is always a straight line. This is shown in the figure. Such

logarithmic or *exponential* curves correspond to an equation of the type—

$$\frac{I_o}{I_t} = e^{-\lambda t} \quad . \quad . \quad . \quad . \quad . \quad (1).$$

In the case under consideration I_o is the initial activity of thorium X, I_t the activity after time t, λ is a constant, and e the natural base of logarithms ($= 2{\cdot}7183\ldots$).

The recovery curve is the inverse of this curve, and is represented by the equation—

$$\frac{I_t}{I_o} = 1 - e^{-\lambda t} \quad . \quad . \quad . \quad . \quad (2),$$

where I_o is the final activity (the maximum figure obtained), I_t the activity recovered after time t, and λ is the *same constant* as in the previous equation.

These results have been given in some detail because they are typical of most of the curves obtained by plotting the change of activity against time. In all cases the decay curve of the *radioactive child* bears the relation to its *radioactive parent* that the constant λ is the same for the two cases. The curves illustrate two further points. They approach constant value towards the end of a month, but it is seen that they reach a final value only at infinite time. This property is common to all such curves; it illustrates the fact that the *life* of a radioactive element is infinite. In order to compare such lives we therefore speak of the *half-life period*, a definite value for each element. It represents the time in which half the element disintegrates; its activity falls to half value. This time can be calculated graphically from the curves, or from equation (1), since the activity has fallen to half value, $I_o = 2I_t$, *i.e.* $2 = e^{-\lambda t}$. Hence if λ is known, t can be calculated. Again, λ represents the proportion of atoms changing per unit of time; $1/\lambda$ thus represents the *average life* of an atom of the element under consideration. A discussion of the meaning of these terms is given in Section 3 (p. 538). In the case of thorium X the half-time is four days.

Hahn has recently shown that thorium at first disintegrates into **mesothorium**, and this into **radiothorium**; the last named is the immediate parent of thorium X. Radiothorium is very much more active than the thorium from which it is derived. The methods employed were similar to those just described—

chemical separations, followed by measurement of the radioactivities of the different products.

Early workers on thorium noticed that the amount of radiation given off was subject to variation. Owens, in 1899, traced this inconstancy to air-currents passing over the surface of the thorium. Rutherford, next year, showed that it was due actually to a gas—hence the effect of air-currents. It could be drawn through tubes along with a current of air, passed through cotton-wool, bubbled through solutions, and gave thereafter an electrical effect. It thus behaved in every way like a true gas, although it could not be isolated, and could only be tested by its radioactive properties. Rutherford termed it an **emanation**. It has a very short-life period. Its decay was studied by drawing it into a cylinder by an air-current, closing the cylinder, and noting the radioactivity from time to time by the electrical method (the cylinder containing insulated metallic discs connected to an electrometer). Its half-life period is 54 seconds.

This emanation of course disintegrates into something else. When some quantity of it is allowed to decay in any closed vessel, the products are deposited on the walls of the vessel. They themselves give off radiations; the phenomenon is known as *excited* or *induced activity*, the deposit as the *active deposit*. It differs in chemical and physical properties from all its predecessors. The emanation can be washed out with air, and the decay rate of the deposit studied. The curve is complex; mathematical analysis indicates at least two products. These were postulated as **thorium A** and **B**. They were differentiated more clearly by the work of Miss Slater, who studied the effect of temperature on them. A platinum wire was exposed for a considerable time to the action of the emanation, whereby (relatively) a considerable amount of the after-products was deposited on it. It was then heated by an electric current. A lead cylinder surrounding it caught any volatilised matter. Both wire and cylinder were then tested separately by an electrometer, the decay of the radioactivity being studied. Heated to about 700° C. the amount of radioactivity on the wire remained constant, but the decay rate was faster than usual. The cylinder was at first only very slightly active, but the activity grew rapidly, the maximum being reached in four hours; the decay rate thereafter was normal. These

phenomena were easily explained by the hypothesis that thorium A, the first product, volatilised below 700° and was *inactive—i.e.* gave no radiations; the thorium B, already produced from it, remained on the wire unvolatilised at 700°, and a fresh amount was slowly produced on the lead cylinder. Further work has slightly modified this result, thorium A being found to have a very slight radiation, and there being two later products, thorium B and C, all three having an extremely short-life period. The final product is inactive. So far as present knowledge indicates, the whole series is:

Thorium → mesothorium → radiothorium → thorium X → thorium emanation → thorium A → thorium B → thorium C → inactive product.

Most of the above work has been accomplished by what may be described as the *direct method* of work. In addition an indirect method, based on chemical means, is frequently employed. It will be discussed more particularly in the subsequent parts of this paper. An example will be mentioned here.

The final product of the uranium-radium disintegrations is supposed to be lead, another product being helium. Boltwood has analysed a great number of uranium minerals; they all contain lead. He finds that the ratio, amount of uranium to amount of lead, varies with the age of the mineral, the older rocks giving a higher percentage of lead. This agrees with the theory that lead is slowly produced from the uranium and radium. Strutt has analysed thorium minerals for helium; he finds evidence of some definite relationship between the quantities of thorium and helium which they contain.

Section 2.—Nature and Properties of the Radiations from Radioactive Elements

When an electric current is passed through a highly exhausted vacuum tube, three kinds of rays are produced in it. If the cathode is perforated, *canal rays*—so named by Wien—are projected with enormous velocity in the direction opposite to that in which the current is travelling; they consist of particles, each at least as heavy as a hydrogen atom, and always carry a positive charge of electricity. *Cathode rays*, consisting of negative particles of electricity, convey the current from cathode to

anode, while *Röntgen rays*, undulations in the ether, are projected in all directions. To these three kinds of ray correspond the three radiations which are emitted by radioactive matter. Like the canal rays are the *α rays*, heavy particles carrying a positive charge; the *β rays* are electrons like the cathode rays; while the γ rays strongly resemble Röntgen rays.

They are frequently emitted simultaneously from active preparations. Two properties allow of their study and differentiation:

(1) They behave differently under the action of a magnetic field;

(2) Different kinds of rays penetrate matter to very different degrees.

Under ordinary conditions all these rays, like light rays, travel in straight lines. Under the action of a very strong magnetic field the path of the α rays becomes slightly curved; β rays are much more easily deflected, and, moreover, in the opposite direction to α rays—compare the fact that α rays carry a positive charge, β rays a negative one; γ rays are not deflected by a magnetic field.

The difference in penetrating power is well shown by the following table (Rutherford, *Radioactivity*, p. 111):

Radiation.	Thickness of Aluminium in cms., which cuts off half the radiation.	Relative power of penetration.
α-rays	0·0005 cms.	1
β „	0·05 „	100
γ „	8 „	10000

These ratios are only approximate; rays from different material have greatly varying penetrative power. Different substances absorb them in widely different amounts; the density of the substance is a factor in determining the amount of absorption.

The radiations—as has been pointed out in Section 1—produce ions in the gases they traverse; the mechanism is collision. Their ionising power varies very greatly, being roughly the inverse of their penetrability.

The enormously greater ionising power of the α rays supports the theory that they are heavy particles shot off from

the disintegrating atoms at enormous velocities. Such large particles cannot travel far without colliding with gas particles, hence their small penetrative power. Their enormous momentum produces the correspondingly great ionising effect actually observed. Rutherford has measured the velocity of α particles from different active elements; it varies from $1{\cdot}56 \times 10^9$ cms. per second in the case of radium to $2{\cdot}25 \times 10^9$ cms. per second for thorium C. Light travels at about 30×10^9 cms. per second. The experiments lead to the conclusion that the substances possessing longest life, viz. uranium and radium, emit particles having the least velocity; the shorter the life the greater the velocity of the emitted α ray. Rutherford has been able to measure the mass of the particle which carries unit charge of electricity; it is about twice that of hydrogen. From this he concludes that the α particle consists either of a half atom of helium (atomic weight 4) carrying one electric charge, or a whole atom carrying a double charge. The α rays carry a positive charge—their mass and velocity correspond very closely with those of canal rays; their close resemblance to these must be held as established.

The β rays have a greater range of velocity. The maximum velocity approximates to that of light (200,000 miles per second). Their identity with cathode rays has been established on three grounds: (*a*) the negative electric charge carried by both; (*b*) the ratio of that charge to the mass—extremely small in both cases—which carries it; and (*c*) the fact that a magnetic field has precisely the same effect in both cases.

α and β rays are completely absorbed by covering the radioactive matter producing them with a layer of lead 1 cm. in thickness. But even if a layer of 1 inch is used, rays still pass through. They carry no charge of electricity, and are not deflected by a magnetic field, yet they ionise gases, and so affect an electrometer. These are the γ rays, ether waves, corresponding to X-rays, but of even greater penetrating power.

All three kinds of rays on impinging on solid particles give rise to *secondary rays*, as do ordinary X-rays. The secondary rays also travel in straight lines, and otherwise obey the light laws, but are deflected by a magnetic field. They resemble cathode rays in being electrons, but move with comparatively small velocity. Ultra-violet light allowed to fall on the surface of metals produces a similar phenomenon.

In examining a radioactive substance to find what kind of radiations it gives rise to, the method in use is to cover it with varying thicknesses of aluminium. Absorption takes place to different extents; the ionisation varies accordingly; this is recorded by electric measurements. From a study of results thus obtained it can usually be determined whether one or more kinds of ray are present; the results are confirmed by noting the action of a magnetic field on rays which have penetrated the different thicknesses of metal.

The radiations produce a considerable number of effects—physical, chemical, and physiological. One of the most important is the phosphorescence induced in many substances subjected to bombardment by the rays. Zinc sulphide, a particularly good example, is rendered luminous by both α and β rays. Crystals of the different platinocyanides give different colour effects according to their composition. The lithium salt phosphoresces pink, the calcium and barium salts deep green, the sodium salt yellow. Willemite, a zinc silicate, becomes beautifully green in colour and apparently translucent. Kunzite shows a red phosphorescence under the action of β and γ rays; α rays are without effect on it. All strongly radioactive compounds phosphoresce strongly themselves.

The diamond not only phosphoresces when bombarded by radium rays, it also changes colour. Sir William Crookes found that a yellow diamond, after seventy-eight days' exposure to the rays, became bluish green. Prof. Bordas has recently experimented with uncoloured rubies; after some weeks' exposure they became dark brown, and in some cases pink; sapphires similarly change colour. The effect is in all these cases probably due to the action of β rays, and is analogous to their action on different glasses. Soda glass is coloured deep violet, potash glass a dark brown, gold glass ruby colour. Similar effects are produced by cathode rays in vacuum tubes. The colour is discharged quite easily by heating the glass to 300–400° C. Maxwell Garnett has made a detailed study of these phenomena, and his work supports the hypothesis that metallic ions are actually liberated in the glass, and that the colour is due to these, violet for sodium, brown for potassium, and so on; application of heat causes recombination with accompanying loss of colour. It should also be mentioned that glass tubes containing radium emanation show a beautiful

green phosphorescence. Under similar conditions quartz glass shows a fine electric blue colour.

The rays change oxygen into ozone. Hence all dry radium salts smell strongly of ozone. In water this effect is not produced, hydrogen peroxide being formed instead. Radium salts and its emanation decompose water. The emanation also effects the recombination of hydrogen and oxygen. These phenomena are in all probability produced by the α rays.

Under the action of β rays yellow phosphorus is converted into the red variety, while iodine is liberated in iodoform solutions. Much work yet remains to be done in this branch of the subject.

Radium rays, like X-rays, produce painful burns. Painful irritation is caused, then inflammation lasting from ten to twenty days. The skin finally peels off. The physiological effects of radium emanation have been tried on mice and guinea-pigs. Long exposure to such treatment is in most cases harmful, in some fatal. Radium rays have a beneficial result in the case of ulcerous growths, but do not cure true cancer. Their effects are thus similar to those of X-rays, but they have the advantage that the radium preparation, enclosed in a small tube, can be applied locally. The medicinal effects of many natural waters are supposed to be due to the presence of small quantities of radium emanation. They are slightly radioactive. Artificial waters of exactly the same chemical composition do not possess the same beneficial effect.

Section 3.—Life of a Radioactive Element

A typical radioactive element gives rise continually to a radioactive product, together with one or more kinds of rays; radium gives rise to its emanation, and to α rays. In addition, heat in comparatively large quantity is continually liberated.

This continuous production of both energy and matter is explained by Rutherford by the assumption that atoms of the parent element are continually being broken down, or disintegrated, into simpler atoms, the heat and rays being the difference in energy-content in the two atomic systems. When guncotton is exploded a complex molecule is broken up into simpler ones, heat and light being also emitted. The two cases are parallel, the one being atomic, the other molecular.

It is found that the emanations, and many other active products, lose their activity almost completely in a measurable time. From studies of the rate at which the activity is lost, the conclusion is reached that in any one time a certain fixed proportion of the total number of atoms present spontaneously disintegrates. An actual illustration will make this clearer. The activity of any fixed quantity of radium emanation falls to half the initial value in approximately four days. In the second four days it falls to half of this second value, *i.e.* one quarter of the original. We therefore suppose that the emanation has decomposed to a corresponding extent. In the unit of time chosen, four days, the same quantity, one-half the amount at the beginning of that period, always disappears. Similarly in any other definite period of time a certain quantity, bearing a definite ratio to the original amount, will disappear. Again, at the end of eight days one quarter of the whole amount remains; at the end of twelve days, one-eighth; of sixteen days, one-sixteenth. But at the end of infinite time there will always remain some quantity, however small. Similarly in all cases of active matter some remains undisintegrated after infinite time; the radioactive elements have an *infinite life.* Though they may have *died* for all practical purposes at the end of some measurable time, an unmeasurable but definite amount remains. However, it has been shown in Section 1 (p. 532) that we can always find when half a given quantity of active substance has disappeared. And it is this period which is termed the *half-life period* of such substances. It varies from four seconds in the case of actinium emanation to millions of years in the case of uranium.

Another term constantly used is the *average life* of a substance. In Section 1 the method of calculating it has been given (p. 532). It can be conveniently illustrated by a human parallel. A church filled with people on any fixed date contains a fair assortment of men, women, and children of all ages. If we know the total number of years each person will live after leaving that church we can calculate the *average life* of the congregation counting from the definite time fixed by that church attendance. This is quite different from the *average life* of some number of persons from the time of birth of each, which is the basis of the data employed to calculate insurance rates.

The *average life* of a radioactive element at any definite time corresponds to the first of these illustrations. If we take a definite quantity of radium salt, then the atoms of radium it contains are of all ages. If they have just previously been separated from their uranium ore some may have been *born* only a few weeks previously, others have existed thousands of years, just as the church congregation may include infants and old men of ninety. Of the radium atoms a certain number will *expire* in a definite time, just as in so many years a number of the worshippers will have died. And we can calculate the average life of the congregation of atoms with as much certainty as that of people.

The application of the second kind of *average life* to radioactive substances was recently worked out in some detail by Sir William Ramsay as a lecture illustration. Though it has just been stated that the life of a radioactive atom is infinite, yet infinity is only a relative term; in this connection it only means a longer time than we can measure. It is extremely probable that just as the human life is measurable and definite, so is, let us say, the life of an atom of radium. One may go further. For there is much more regularity in the life of this dead matter; the life of human beings is variable, dependent on "all the ills that flesh is heir to," microbes, the bearers of disease, and accidents, the ills of fortune. We have no ground to suppose that the life of a radioactive atom varies from any similar cause. For example, the rate of decay—the death-rate—of radium emanation is unaltered within the limits of measurement between the temperatures of $-180°$ and $+1600°$ C. ($90-1870°$ in the absolute scale), the extremes at which, so far, it has been experimentally tested. If this tremendous difference of temperature does not hasten the decay of a single atom of emanation we can at least postulate that its life is not easily influenced by external causes. So far experimental work has shown that we cannot hasten or retard the death of a radioactive atom; consequently we cannot alter its life. For its birth is but the death of its parent atom, to which the preceding statement likewise applies. And we are justified in stating that the average life of a radioactive atom, as used in the second sense above, is in all probability the actual life of that atom.

Section 4.—Radioactive Elements and their Properties

No fewer than twenty-four new elements have been discovered by radioactive methods; uranium and thorium were known long before their activity was observed. Of these twenty-six elements, five are said to be *rayless*; in them no activity has been detected by the instruments in use at present. The others emit one or more kinds of ray; nine or ten give α particles alone. An appreciable life-period is possessed by nine only—uranium, thorium, radium, polonium, radio-lead, mesothorium and radiothorium, actinium, and probably ionium. The remainder are none the less true elements, although their short life may never permit them to be examined by other than radioactive means.

If the recent work of Boltwood is correct, and ionium is the true intermediate product between uranium X and radium, these twenty-six elements fall naturally into three large groups, namely, the elements uranium, thorium, and actinium, and their respective disintegration products. Using Rutherford's method of classification (from *Radioactivity*, pp. 449-50) in a slightly modified form, the elements can be grouped as shown below. Only the atomic weights of three—uranium, radium, and thorium—are known with any certainty. If the α particle is a helium atom (of atomic weight 4), then the atomic weights of the other elements, calculated by deducting 4 for each α particle evolved, may approximate to those given in brackets. The present state of our knowledge does not allow any stress to be placed on this hypothesis. In the table on the next page Ur = uranium, Th = thorium, Ra = radium, Act = actinium.

The nomenclature of the elements is due to Rutherford; his original idea was to name the first derivatives so as to show their parentage; hence Ur X, Th X, Act X (ex-uranio, ex-thorio, ex-actinio). The discovery of radiothorium and radioactinium upset this system. It will be observed that each group contains one gas or emanation; the elements derived from it are named in order of formation A, B, C, and so on. The graphic representation in the last column, due to Rutherford, illustrates the method of disintegration, the atomic contractions due to loss of α particles being considerably exaggerated in order to emphasise the theory. The brackets show those elements which differ in mass content by not more than one electron.

Element.	Atomic Weight.	Half-Life Period.	Nature of Emitted Rays.	Exaggerated Graphic Representation
First Group:				
Ur	238·5	—	α	
↓				
Ur X	(234·5)	22 days	$\alpha\beta\gamma$	
↓				
Ionium	(230·5)	—	$\alpha\beta\gamma$	
↓				
Ra	226·5	1300 years or 164 ,,	α	
↓				
Emanation	(222·5)	3·8 days	α	
↓				
Ra A	(218·5)	3 minutes	α	
↓				
Ra B	(214·5)	21 ,,	rayless	
↓				
Ra C	(214·5)	28 ,,	$\alpha\beta\gamma$	
↓				
Ra D	(210·5)	40 years	rayless	
↓				
Ra E	(210·5)	6 days	$\beta\gamma$	
↓				
Ra F	(210·5)	143 ,,	α	
↓				
Inactive Product	(206·5) Cp. lead = 207	—	rayless	
Second Group:				
Th	232·5	—	rayless	
↓				
Mesothorium	(232·5)	5·5 years	β	
↓				
Radiothorium	(232·5)	737 days	$\alpha\beta\gamma$	
↓				
Th X	(228·5)	4 ,,	α	
↓				
Emanation	(224·5)	53 seconds	α	
↓				
Th A	(220·5)	11 hours	slow β	
↓				
Th B	(220·5)	55 minutes	$\alpha\beta\gamma$	
↓				
Th C	(216·5)			
↓				
Inactive Product	(?)		rayless	
Third Group:				
Act	?	—	rayless	
↓				
Radioactinium		19·5 days	α	
↓				
Act X		10·2 ,,	α (β?)	
↓				
Emanation		3·9 seconds	α	
↓				
Act A		36 minutes	rayless	
↓				
Act B		2·15 ,,	$\alpha\beta\gamma$	
↓				
Act C		?		
↓				
Inactive Product		—	rayless	

A short account of the individual elements will now be given, in the order shown opposite.

Uranium was discovered by Klaproth in the mineral pitchblende in 1789. It is of comparatively rare occurrence, and widely scattered. The composition of uranium minerals varies largely; many are complex silicates, phosphates, or arsenates. Pitchblende and uraninite consist largely of uranium oxide, and contain from 50–80 per cent. uranium. The metal was isolated by Peligot in 1842 by the action of potassium on the fused oxide. Thus formed it is a black powder. In the ordinary metallic state it closely resembles iron and nickel. Heated to redness it burns brilliantly. It dissolves in dilute acids, with evolution of hydrogen; combines directly with chlorine, and, on heating, with sulphur. Its atomic weight is 238·5; it is thus the heaviest metal yet isolated. A great number of its compounds have been prepared. The discovery of radioactivity by Becquerel, in 1896, was made with these compounds; it has been shown that the metal is also radioactive. The life of uranium is extremely great. Its half period is many millions of years.

In 1900 Sir William Crookes showed that when excess of ammonium carbonate is added to a uranium solution, until the uranium precipitate has all redissolved, a light cloudy precipitate remains: this contains all the photographic activity; the separated uranium is without effect on a photographic plate (α rays do not affect a photographic plate; uranium gives off α rays only); Crookes called the new product **uranium X**. The precipitate consists largely of impurities from the uranium salt, and insufficient uranium X has been obtained to give a distinctive spectrum. A mixture of ether and water effects a partial separation. The ether layer contains most of the photographic or β-ray activity. Becquerel effected a separation by adding barium chloride and precipitating the barium as sulphate; uranium X is carried down along with it. Recently (in 1906) Moore and Schlundt have described further methods of separation. When crystallised uranium nitrate is dissolved in acetone, or several similar organic solvents, the slight precipitate which remains contains most of the uranium X. Complete separation is effected by adding moist ferric hydroxide to such a solution; the hydroxide carries down all the active matter. Moore and Schlundt state that uranium X gives both α and β rays; 34 per cent. of the activity is due to the α-rays. Levin

in 1907 obtained the figure 8 per cent.; in a later paper he states that no α rays are produced, the mistake arising from the presence of β rays of small velocity. The question has not yet been decided. Uranium X has a half-life period of twenty-two days. In less than a year it has disintegrated almost completely. Into what has it changed?

Ever since Madame Curie succeeded in obtaining radium from uranium minerals, and the theory of disintegration was put forward, it has been considered highly probable that radium is a *descendant*, in perhaps the third or fourth generation, of uranium itself. Some experiments of Soddy in 1904 gave the first proof of this statement. He took about two pounds of uranium nitrate, dissolved it in water, and repeatedly added barium solution, precipitating the barium as sulphate. In this way the solution was practically freed from radium, which is precipitated along with the barium sulphate. In 567 days the solution contained more than one hundred times as much radium as it did immediately after this treatment. This radium was identified by the decay rate of its emanation. The actual amount of radium observed was only one-thousandth of what it should be on the assumption that uranium X was the parent of radium. Soddy postulated one or two intermediate products. Boltwood criticised his method of procedure but afterwards confirmed his results. In 1906 he suggested that the intermediate product was actinium. Soddy and Mackenzie, and also Rutherford, showed that this was impossible, pure uranium nitrate neither giving rise to actinium nor its emanation. Rutherford separated the actinium from solutions of commercial uranium nitrate, and by passing ammonia and sulphuretted hydrogen gases through the actinium solution, he effected the separation of a new radioactive substance, which he considered to be the actual intermediate product between uranium X and radium. Boltwood confirmed this result. He found this new element emits α rays (actinium is rayless) which are very easily absorbed, and β rays of small penetrability. The activity is of the same order as that of radium. He suggested the name **Ionium**. Hahn has confirmed his conclusion by a different method.

Radium was discovered by Madame Curie in 1898. Her method of procedure has been indicated. Thoroughly examining the different group precipitates in an analysis of pitchblende, she found that the barium group precipitate was strongly active.

This activity could be completely separated along with barium sulphate. Final separation was effected by recrystallising the barium as chloride; radium chloride is slightly less soluble and separates in the first fraction. In this way crystals were finally obtained nearly two million times as active as uranium. The activity was too great for comparative measurements; the final fractions were tested for purity by estimating the amount of barium spectroscopically.

Giesel showed later that the separation could be effected more conveniently by recrystallising the bromides; the difference in their solubilities is greater than in those of the chlorides.

Radium continually gives rise to a gas, the **Emanation from Radium**, discovered by Dorn in 1900, and no intermediate product has yet been detected. A full account of the properties of radium and its emanation will be given in Part II. of this paper.

When any substance is exposed to the action of the emanation it becames coated with an intensely active deposit. This was first observed by M. and Mme. Curie in 1899. It is known as the **active deposit of rapid change**, and has been found to consist of three consecutive products, **Radium A, B, and C.** The whole activity decays to half value in 28 minutes, but the decay curve is very irregular. Studies of the rates of decay of the different rays led to the analysis into three separate elements. All three are soluble in strong acids, and volatile at a white heat. B is volatile at the lowest temperature, and can be thus partially separated.

In 1903 the Curies also observed that substances which have been covered with this active deposit do not lose all their activity after even a prolonged period. Giesel confirmed this. Rutherford found that the activity increases during several years. It is due to the **active deposit of slow change**, which has been resolved similarly into three consecutive products, **Radium D, E, and F.**

Radio-lead (or Radium D) was obtained by Hofmann and Strauss in 1901. The lead obtained from pitchblende was strongly and permanently radioactive—hence the name radio-lead. In 1904 Hofmann and co-workers showed that the lead itself is not radioactive, but gives rise to active products separable by chemical means; the inactive lead slowly regains activity. It therefore contains an inactive element which disintegrates slowly into active products. Rutherford has proved fairly conclusively the identity of the rayless parent, the true radio-

lead, with radium D, and of the active products with E and F. He found that the activity of the short-life deposit from radium practically vanished after two days; thereafter there was a slow increase during eighteen months. The new activity was due to both α and β particles. Two experiments showed the nature of the changes. A deposit on a platinum wire, after standing for some considerable time, was subjected to the action of heat. Below 1000° it was unaffected. Between 1000° and 1050° some part volatilised. It no longer gave off α particles, while the β-ray activity decreased rapidly, falling to half value in six days. During the same time α rays were emitted in slowly increasing amounts.

Clean surfaces of metallic bismuth placed for some time in solutions of the slow-change deposit removed 90 per cent. of the substance emitting α particles. The bismuth thereafter emitted these α particles, activity decreasing somewhat slowly; the half-life period was 143 days. The β-ray activity of the solution remained unaltered by this treatment; after the bismuth was taken from the solution the latter commenced slowly to emit α rays.

A simple explanation is given by the assumption of three elements: radium D (rayless); E, giving β rays only; and F, giving α rays only. D is volatile below 1050°; E does not volatilise at that temperature. D is the parent of E, for after it has volatilised the amount of E rapidly becomes less. F volatilises at 1050°, for the wire loses its α activity. It is produced from E, for the α activity of the wire is slowly regained. F, alone of the three, is deposited on bismuth from solutions, and it is the element whose half-life period is 143 days.

Meyer and Schweidler consider that this hypothesis does not completely satisfy the peculiarities of the curve of decay. They suggest a further intermediate product (thus RaE_1 and RaE_2).

Rutherford has shown the identity of **polonium, radio-tellurium,** and **radium F**. Polonium was the first radioactive substance discovered by Madame Curie. The sulphide precipitate from acid solutions of pitchblende contained an active substance, which associated itself with bismuth. With this element its properties are so closely allied that it is impossible to effect a complete separation. Madame Curie repeatedly precipitated the nitric-acid solution by water. The precipitate contains most of the active material. Marckwald obtained the same substance by dipping a rod of bismuth or antimony in the

active solution. These formed an intensely black deposit, chiefly tellurium, and very active; he named the active matter radio-tellurium. Dissolved in hydrochloric acid, all the tellurium was precipitated by hydrazine hydrochloride; the active matter remained in solution. By repeating the process, Marckwald obtained a few milligrams of intensely active material.

There remains the question of the final product. Radium F decays at a moderately rapid rate. What becomes of it? Two lines of argument point to the conclusion that **lead** is formed. On the assumption that the α particle is helium of atomic weight 4, then, since α particles are given out by radium and four of its products, the atomic weight of the final product should be $226{\cdot}5 - (5 \times 4) = 206{\cdot}5$. Lead has the atomic weight 207, a very close agreement.

Again, Boltwood has shown that lead is present in all uranium-radium minerals, and the amount is greatest in the oldest—*i.e.* those in which the greatest quantity of uranium has disintegrated. This also points to the fact that the lead is derived from uranium, and therefore from radium.

Thorium was discovered by Berzelius in 1828. It occurs chiefly in Ceylon, the recently discovered mineral thorianite containing more than 70 per cent. of it. It is precipitated from solution by ammonia, and usually separated in the form of oxalate. The metal has been prepared as a grey powder; it burns brilliantly in air, and is easily dissolved by warm, dilute acids. The oxide ThO_2 is usually obtained by calcining the oxalate or sulphate. A large number of the salts have been prepared.

An account of the disintegration changes of thorium has been given in Section 1 (pp. 530-534). It need only be mentioned here that the emanation is an inert gas strongly resembling the gases of the argon group, while the activity of radiothorium is several hundred thousand times that of thorium itself. Rutherford suggests that the final disintegration product of thorium may possibly be bismuth.

Actinium was discovered by Debierne in 1899, and independently as *emanium* by Giesel in 1902; it is precipitated with the group of cerium earths, and is closely allied to lanthanum. It is many thousand times more active than thorium; although it strongly resembles that element, yet all the products of the two have entirely different decay rates—a sufficient proof of their separate identities.

Hahn, in 1907, succeeded in showing that actinium is rayless, its activity being due to its first product **radio-actinium**; this gives *a* rays only, corresponding to radiothorium. According to Giesel it resembles the alkaline earth metals, and can be precipitated from actinium solution by means of finely divided sulphur. It disintegrates into **actinium X**, independently discovered in 1905 by Giesel and Godlewski; the separation is similar to that employed for thorium X. The emanation was observed by both Debierne and Giesel; Godlewski proved that actinium X was its immediate parent. Debierne has recently noted the production of helium from this emanation; Giesel has confirmed the statement. The analysis of the active deposit from the emanation is in great part the work of Miss Brooks. Her work led to the recognition of **actinium A** and **B**; Meyer and Schweidler consider that **C** and **D** also exist.

So far we have no clue to the atomic weight of actinium. But it corresponds to lanthanum; in that case it either comes between radium and thorium, with an atomic weight of about 230, or has a greater weight than uranium. Actinium emanation most probably belongs to the argon series, in the periodic system, when it follows that radio-actinium corresponds to radium (it resembles the alkaline earth metals) and actinium X occupies the space below gold. With similar treatment of the thorium products we can postulate some such arrangement as the following for the higher members of the periodic system; it accepts the simplest hypothesis of disintegration—that it is accompanied by loss of mass.

Kr 87·8	Rb 85·4	Sr 87·6	ϒ 89	Zr 90·6	Cb 94	Mo 96	...	Ru 101, Rh 103, Pd 106·5
...	Ag 108	Cd 112·4	In 115	Sn 119	Sb 120	Te 127·6	I 127	...
X 128	Cs 133	Ba 137·4	La 139	Ce, etc., 140-178	Ta 183	W 184	...	Os 191, Ir 193, Pt 195
...	Au 197	Hg 200	Tl 204	Pb 207	←RaF← Bi 208·5	(?RaE)←	(??RaD)← ?← ?←	(RaC)←(RaB) ←(RaA)← (ThC)←(ThB) ←(ThA)← (ActC)←(ActB) ←(ActA)←
Ra Em ← Th Em ← Act Em←	← Th X ← Act X←	Ra 226·5 Radioth ← Radioact←	← Mesoth ← Act	Ionium← Th 232·5	UrX ←	U 238·5		

There are several difficulties in the way of accepting such a scheme. For example, radium D has given no indications of any resemblance to the halogens; on the contrary it strongly resembes lead. Although such hypotheses must therefore be put forward very tentatively, we can scarcely evade the conclusion that many higher members of the series have almost coincident atomic weights, while there are several cases of at least two elements occupying one space in the table. Thus, considering the radium and thorium products alone, their emanations are both inert gases strongly resembling the argon gases. To move one a space higher in the series, the difference in their atomic weights must be at least 25. If the hitherto published chemical work on the atomic weight of radium is in any way near the truth, this cannot be the case. Similarly radium F must have an atomic weight less than radium, and it closely resembles bismuth in all its properties. If the atomic weight of radium is 226·5, it seems certain that bismuth and radium F must occupy the same space. There are only two other possibilities. A somewhat similar table, put forward by Meyer and Schweidler in 1906, assumes that uranium contains in reality a second element of much greater atomic weight, about 260, and that radium has the corresponding weight 255. In the second place, disintegration may result in the combination of two or more atoms of the product, giving an element of higher atomic weight; in this case, the active elements will not appear in consecutive series in the periodic table.

The second part of this paper will contain a full account of radium and its emanation.

The third part will include a description of the experimental production of transformation or transmutation of elements.

THE ACTION OF ALCOHOL[1]

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It is but seldom in the study of medical science that one has to treat of a question of such widespread interest, and, as I believe, of such paramount national importance as we have before us to-day, and it is to be deplored that the medical profession has hitherto been able to answer only with uncertain voice, or, I might say, with two voices, the persistent demand for its opinion of the value of alcohol in therapeutics and in diet.

This fatal lack of unanimity is to be ascribed in the first place to the feeling that alcohol has not proved devoid of usefulness in therapeutics in the past, and that we must not be hurried into its dismissal from the sphere of medicinal agents without due consideration; and the denial of its value in disease has been in many cases too absolute, and has, in fact, provoked a reaction in its favour in some minds that were perhaps prepared to accept a more restricted use of alcohol as a remedy than has hitherto prevailed. The greatest possible advance in the crusade against the abuse of alcohol would be made, I think, if we could agree upon some formula that could be generally accepted, and I am not without hope that this meeting may make some progress towards this solution.

Another cause of confusion in the response of medicine to inquiry regarding the value of alcohol arises from ambiguity in the use of terms. We are too apt to apply the term "stimulant" to anything that promotes exhilaration and animation, and dissipates what the eighteenth century called the spleen, and to regard the result as evidence of health and vigour. But stimulant is also used, in a more exact sense, to indicate anything augmenting the activity of definite organs. It would, I think, conduce to more general agreement if the word could

[1] A paper read before the Section of Physiology at the British Association, Leicester, 1907.

be used strictly in this narrower sense in discussing the question of alcohol, and if its effects, beneficial or otherwise, were always referred to each individual organ.

Alcohol affects so many functions of the body that it is impossible to take them all up in the time at my disposal, and I shall therefore limit my observations to its action on nutrition, on the brain, and on the circulation.

Its effects on nutrition are ascribed in part to its influencing the digestion and absorption of ordinary foods, and in part to its acting as a food itself. As to the first, its effects on the digestive processes, there is a very general belief, supported by apostolic authority, that alcohol improves digestion. A large number of painstaking investigations have been carried out without fully confirming the popular view, however. It is true that the digestive ferments have been found to be accelerated by very small quantities of pure alcohol, but the acceleration is very small in degree, and is not observed when the forms of alcohol in ordinary use are substituted for the pure spirit, nor when this itself is added in quantities corresponding to one to two glasses of whiskey in man. As to the secretion of the digestive fluids under alcohol, it has been repeatedly found that alcohol after absorption induces a flow of gastric juice, but this is devoid of, or poor in ferments, and can scarcely promote the preparation of food for absorption. The movements of the stomach and intestine may perhaps be more active after alcohol has been swallowed in a concentrated form, and this may perhaps be the basis of the after-dinner liqueur. And some evidence is presented that alcohol accelerates absorption from the intestine, as is true of many other slightly irritant bodies.

The effects of alcohol on the digestion are therefore complex, for almost every factor in the process is altered in activity to a small extent when moderate quantities are taken. When one remembers, in addition, that the greatest influence of all on digestion is exercised by the taste and odour of the food, one is prepared for great divergences in the effects of alcohol in man. And this is the only inference that can be drawn from the results of clinical inquiry as to the value of alcohol as a stomachic in man. In some people the progress of digestion seems to be rather improved when wine is taken, but the improvement is small, while in others the reverse is true: the digestion is not accelerated, and may even be retarded by a

couple of glasses of wine. The actual amount of food absorbed from the alimentary tract is scarcely changed definitely in either direction. But however variable the reaction of the individual stomach to small quantities of alcohol may be, there is only one response when larger quantities are taken, and that is disorganisation of the whole process. And while the usefulness of alcohol in treating some digestive disorders may still be uncontroverted, Binz's dictum, that the healthy stomach needs no stomachic, and therefore no alcohol, must be the standpoint of the physician to-day.

But it may be argued that while the absolutely normal stomach is capable of digesting thoroughly and extracting the whole of the nutriment from the food offered to it, the artificial conditions under which most of us live necessitate measures which are unnecessary in a more healthful environment. Does not the jaded appetite demand exceptional measures, and may not wine be used to render food palatable and promote gastric secretion and digestion just as other condiments are employed? Shall he who seasons his food with wine be condemned, while he who substitutes mustard may be regarded as of upright life and conversation? The objection to the habitual use of alcoholic beverages "for the stomach's sake," in the scriptural phrase, does not arise from its effects on the digestion, but from the tendency towards the habit being formed and from its action on the brain.

In regard to the second phase of the question of alcohol on nutrition—its food value—the last few years have witnessed experiments performed with such meticulous care that there can be but one opinion in the minds of those who have studied the subject. Over 95 per cent. of the alcohol ingested undergoes combustion in the tissues and is utilised by them as a source of energy. As regards its fate in the body, in fact, alcohol is strictly comparable to sugar, which is also an alcohol, though of a more complex nature than the substance under discussion. Like sugar, it is capable of supplying energy, which may be utilised in heat formation and mechanical work, and it may lead to the deposit of fat and to economy of the precious nitrogenous stores of the tissues. In fact, the more closely the metabolism under alcohol is examined, the more closely is it found to conform to that under an equivalent amount of carbohydrate, and it seems to me that the protagonists in the fight against

alcohol can only harm their cause by still refusing to accept these results. For the recognition that alcohol resembles sugars and fats in its fate in the tissues by no means implies that it is a suitable food in disease or in health. The same is true of vinegar and even of morphine under certain conditions. Before an oxidisable substance can be contemplated as a substitute, therefore, it must be shown that, given in quantities which have any significance in calories, it has no greater possibilities for harm than normal foods. Can alcohol be taken without toxic effects on the tissues in general, quite apart from those on the brain and more specialised organs? On this point experiment has shown that when alcohol is substituted for other forms of food in persons unaccustomed to its use, it sometimes fails to act as an equivalent for some days, during which the deficiency has to be made up by the combustion of other available sources of energy. This has been supposed to indicate some specific toxic action of alcohol on the tissues; but there are grounds for believing that alcohol does not stand alone in this relation, but that the same phenomenon occurs when other unaccustomed but unimpeachable forms of food are suddenly substituted for those which the tissues have hitherto consumed. In this point, then, alcohol appears to behave in the same way as other nitrogen-free foods.

But another series of investigations has shown that alcohol leaves the tissues in an impaired state in regard to the measures which the organism normally takes to protect itself from injuries either by living organisms or by poisons. No experiments were needed to show that the abuse of alcohol lessens the resistance to invasion by pathogenic organisms; the records of pneumonia in our hospitals and of cholera in the East indicate this beyond the shadow of a doubt. But these fail to show beyond question that the habitual use of alcohol in small quantities, or its therapeutic use, has this effect; and the whole interest of the question at present lies in the dietetic use of alcohol as contrasted with the drunkard's abuse of it. A number of animal experiments on the subject have been performed by inoculations of pathogenic bacteria, or of their toxines, before or after the administration of alcohol, the mortality being compared with that of animals inoculated in the same way but not treated with alcohol. In these the results have almost uniformly been arrayed against the use of alcohol, but,

unfortunately, the quantities of alcohol given scarcely correspond to the moderate use in man. Even Laitinen gave his rabbits about 1 c.c. per kg., which would correspond to about 4–5 oz. of whisky per day in a man. This quantity was insufficient to cause symptoms of intoxication in his animals, but the corresponding ratio could scarcely be considered within the limits of moderation in man.[1] Some recent work by Reid Hunt bears closely on this question, in that he finds that the continued administration of alcohol in small quantities renders mice and guinea-pigs much more susceptible to the effects of acetonitril, a poison which acts by the liberation of hydrocyanic acid in the tissues. Hunt considers his results due to alcohol deranging the metabolism in certain directions, notably tending towards an acceleration of some oxidative functions. And in this he sees a specific difference between alcohol and the carbohydrates, in that these have of course no such influence on the metabolic processes.

Hunt states that these changes arise from quantities of alcohol which correspond to that indulged in by "moderate drinkers," inasmuch as his animals showed no signs of intoxication. But a drop of alcohol per day for a mouse corresponds to an immoderate use in man; and in view of the importance of his evidence, it is extremely desirable that a more accurate determination of the amounts of alcohol given were available. For while I think there can be no question that alcohol in excess reduces the resistance of the general tissues to disease and may be deleterious to them in other ways, as Hunt's results indicate, it still remains undecided what is the lowest point in alcohol administration capable of inducing these effects.

On the whole, it must be conceded that small quantities of alcohol have not been proved to act deleteriously on the tissues in general, but, on the other hand, the threshold below which alcohol is innocuous has not been ascertained with accuracy, and probably lies nearer the limit of "moderate use" than is generally recognised.[2]

[1] Since this paper was written, a further series of experiments has been published by Laitinen, who finds that the prolonged administration to animals of quantities of alcohol corresponding to less than a glassful of whiskey or two glasses of port wine per day in man, exercise a distinctly deleterious action on the blood, and reduce the resistance to infection.

[2] In view of the statement made by Professor Reid Hunt during the discussion of this paper and the later publication by Laitinen just mentioned. I

The effects of alcohol on the central nervous system differ very considerably in different individuals. In the lower animals they are marked by depression, the symptoms being exactly similar to those of chloral or of the other narcotics. Occasionally, a transient excitation occurs, but this is due to the irritant action in the stomach, and is absent when more dilute solutions are administered, or when the alcohol is ingested in small repeated doses. In human beings the same depressant effect is often seen, the first symptoms being more or less drowsiness and heaviness, which subsequently pass into slumber. But in the majority of cases the first effects elicited are feelings of good fellowship, well-being, and liveliness, with increased confidence in the mental and physical powers. The face is flushed, the eyes bright, and the pulse and respiration are accelerated. Larger quantities lead to uncertainty and inco-ordination of the movements, shown in difficult and stammering speech and staggering gait, and still larger amounts induce sleep and narcosis, which may pass into complete anæsthesia, and eventually prove fatal. The symptoms of intoxication, therefore, appear to differ in the lower animals and in man, for while in the former there are generally no signs of excitement, in the latter this feature may be very marked in the beginning. And even in man the effects of alcohol offer marked contrasts in different individuals, and in the same individual at different times. For the excitement is very much more marked when drinking is indulged in in company with others, while when alcohol is taken with less exhilarating environments or in solitude, the excitement stage is very much less marked or may be entirely absent.

The effects of alcohol on the brain have been explained in two different ways : the view which appears at first sight to be the more natural one, is that it first stimulates the cerebral cells to greater activity and then depresses them ; that is, alcohol is believed to act on the cerebral grey matter in the same way as strychnine on the spinal cord. And this view, that alcohol is a central nervous stimulant, is still widely

feel that this paragraph requires modification. The very moderate use of alcohol (by which I mean the habitual daily consumption of one or two glasses of port, one or two pints of beer, or a glass of whiskey) appears from the researches of these authorities to induce definite deterioration of the tissues, and to render them more susceptible to attack by disease.

entertained both by the laity and by clinicians, while the majority of experimental observers rather lean to the view suggested by Schmiedeberg and supported by Bunge, Kraepelin, and many others, that the stimulation of the brain is only apparent. According to this theory, the excitement is caused, not by the augmented vitality of the nerve cells, but by a loss of the associations which ordinarily retard the expression of mental activity.[1] To adopt a mechanical simile, the brain may be compared to an engine fitted with powerful brakes. An acceleration of the motion may be due either to increased power of the engine (stimulation) or to the brakes being taken off, and it may be difficult for an onlooker to determine which is the true explanation. The apparent evidences of increased mental activity under alcohol, however, have proved for the most part illusory, when carefully investigated. The closer one approaches to the engine, the more evident it becomes that what appeared to be the result of increased power is really the effect of the removal of the brakes.

One argument against the stimulant action of alcohol is the narrow limits to which it is confined. All the recognised central nervous stimulants act on some particular part in small doses, but when larger amounts are ingested the stimulant action spreads over a wider area of the central nervous system, and gives rise to the symptoms characteristic of stimulation of that area. Caffeine, for example, first stimulates the mental functions apparently, but in larger quantities involves the motor sphere of the brain, and may finally stimulate the cells of the cord. Alcohol, on the other hand, appears to have only a depressant action on the nervous tissues, except in the human cerebrum. It is true that the exceptional development of the human brain might permit of a departure which is without analogy in other forms of poisoning.

But when the excitement stage is more closely investigated, it becomes apparent that all the cerebral functions are not facilitated by alcohol. It is common knowledge that under the influence of alcohol an individual may be more brilliant

[1] When it was propounded the rôle of inhibition in the central nervous system was not appreciated, or at any rate had not been experimentally demonstrated. The recent work of Sherrington has, however, shown that every movement involves motor and inhibitory impulses, and seems to give a firm basis for the depression theory of alcohol.

in conversation, more witty, more social, more generous in sentiment, but that he is not so careful in his statements, and has not that consideration for his own position or that of others which he ordinarily manifests.

The normal adult, in an environment which in a child would cause every symptom of exhilaration, maintains his self-control, partly because the position has lost its novelty, that is, he has associations which are wanting in the child, partly because the exuberance and gesticulations natural to the child are kept in check by his sense of the ridiculousness of these manifestations in later years. Remove the inhibiting associations, destroy the self-control of adult life, and the man becomes a child again in his sense of exhilaration and symptoms of excitement. The symptoms of intoxication which are ordinarily regarded as indicating stimulation of the brain do not necessarily involve this interpretation, but may be explained by a removal of those associations which ordinarily inhibit the external manifestations of emotion.

In a word, it is generally recognised that some of the highest functions of the brain are thrown out of action by alcohol administered in quantities which induce the phase of exhilaration. The further question is: What functions are actually increased in activity, and how far is this increase dependent upon the reduced activity of the processes which are depressed by alcohol?

Much valuable evidence as to the effect of alcohol on mental processes has been gathered in the psychological laboratories, especially by Kraepelin and his pupils, who have subjected the question to a large number of ingenious psychological tests. Thus it is found that typesetters do a smaller amount of work and make a much larger number of misprints when even a couple of glasses of beer are allowed, than when they perform their work without this drug. When a student was set to learn a number of meaningless syllables or a row of figures, he took a longer time to do so and made more errors in repeating them under alcohol than normally. Similarly, arithmetical calculations of all kinds were carried out much more slowly and with more errors, and the writing was slower and gave the impression of being that of an uneducated person who seldom had occasion to use his pen. Only in one respect was any increased aptitude shown—namely, in the transformation of

an idea into movement. And many ergographic experiments appear to show that small quantities of alcohol have the effect of temporarily increasing the capacity of doing muscular work, especially when the subject is fatigued. This augmentation is only transient, and the total work done in the course of the day is considerably reduced by alcohol, as has long been demonstrated in the case of forced marching. These might suggest the view that the motor cells are first put in a state of greater activity by the direct action of alcohol on them, but another explanation is equally applicable, namely, that an ordinary movement is hampered by a series of associations, and that when these are destroyed by alcohol the movement may be carried out more quickly. At the same time, the associations in ordinary life not only retard the movement but also restrict and direct it, and the result of their absence under alcohol is shown by the awkwardness and inaccuracy with which the movement is executed.

It is noteworthy that in these experiments those mental processes which were ordinarily performed readily were less retarded than others in which the subject was less practised and which required more effort. That is, the powers most recently acquired and most readily lost are those on which alcohol first acts, while those operations which have become habitual are less impaired. This is in complete accord with what is observed in the earlier stage of intoxication or exhilaration. The most recent acquisitions in adult life are the power of self-control and the feeling of self-respect, which are manifested in regard for the conventions of life, and in the prudence which leads one to avoid many procedures which in earlier life might have been indulged in without reproach. And under alcohol these are the first mental processes to be disordered. *In vino veritas*, in intoxication the natural man is exposed, stripped of the trammels of convention, and robbed of the fruits of experience and education.

Many other results of these experiments are of interest, but cannot be entered on here. One feature which bears a familiar aspect, and which was brought out clearly in many instances, is the confidence of the subject of the experiment that his efforts were unusually successful under alcohol, while the impartial record showed results far below the level attained during abstinence.

In all of these experiments the amount of alcohol taken was small, in no case sufficient to induce any of the more evident symptoms of intoxication. It is therefore of great interest to find in the later publications of Kraepelin's laboratory, that distinct impairment of the psychical powers was found to persist for a much longer time than would be anticipated; the average efficiency was not regained until from twelve to twenty-four hours had elapsed after the alcohol had been taken. If this proves to be true in the case of persons who have acquired a tolerance for alcohol, even moderate drinkers are never completely normal, their mental powers never recovering entirely from one dose of alcohol before the next is taken.

The results of these investigations on the mental state under alcohol, as well as many others which I have not discussed, appear to place the theory that alcohol acts as a narcotic upon a firm basis. I do not hold that it is absolutely determined, but some more satisfactory evidence must be brought forward in favour of the stimulation theory before it can be considered as a rival to that of Schmiedeberg. And this evidence must define what functions are stimulated, and must not be a repetition of the old statement, that the tone and vigour of the nervous system are maintained by alcohol.

But if the chief or even the whole action of alcohol on the brain were proved to be a narcotic one, this would not preclude its use in therapeutics. For here the chief object in the use of alcohol is not to induce but to repress cerebral activity, and the alleged stimulant action arises from a confusion of ideas; a similar confusion is met with in regard to opium, which was also regarded as possessing stimulant properties which recommended its use in acute diseases accompanied by cerebral symptoms. The result of both drugs is in reality cerebral depression, which manifests itself in a condition of euphoria. The disease often loses its strongest ally when the anxiety and worry of the patient are allayed by alcohol. He feels less concern and more resignation, not because his soul rises triumphant through the stimulant action of alcohol, but through his brain being less capable of dwelling on his disabilities, because it is partially narcotised.

Alcohol, therefore, is not to be regarded as exercising any unique action on the brain in disease, but resembles the other narcotics, and as a remedy must be compared with these. And

on the whole it emerges from the ordeal as not inferior in many points. Thus, none of them disturb the digestive tract less, and most of them exercise a more depressant effect on the centres in the medulla oblongata; for I think it may be taken as proved that in ordinary therapeutic doses alcohol does not depress the respiration, but, on the whole, tends to augment it even when no excitement is induced. Where a slight narcosis, sufficient to allay anxiety and induce rest is required, then, alcohol deserves consideration, but it is less certain in effecting a more marked depression, for which it cannot be compared with the modern narcotics.

The effects of alcohol on the circulation have long been a matter of dispute, many clinicians holding that in failure of the heart and vasomotor centre alcohol is of service, while others have found that it may be dispensed with. The experimental results have recently been discussed by Dixon, who suggests that alcohol may support the heart by acting as a food-stuff, and may thus increase the blood-pressure and improve the circulation. It is true that another observer has not been able to satisfy himself that alcohol acts as a food for the heart, but Dixon's results unquestionably re-open the question of the usefulness of alcohol in the treatment of acute circulatory failure, in regard to which a sceptical attitude has more recently been adopted by many of the leaders of the medical profession. And in addition to any direct action on the circulation, alcohol may prove of value in circulatory failure through its narcotic action in the same way as opium, over which it has the advantage of not inducing any embarrassment of the respiration.

To sum up, alcohol may be of some value in therapeutics as an adjuvant to foods, in order to render them more attractive, and thus improve their digestion, and also possesses some food value itself. It acts as a cerebral depressant, and may be useful in certain diseases in this way, and it may perhaps aid the failing heart. A small dose exercises no definite demonstrable poisonous effects on the tissues, and small repeated doses, though suspect, have not been shown to be deleterious.[1] If alcohol were a new synthetic remedy fresh from Germany, it might probably be hailed as a useful addition to therapeutics, but its popularity as a remedy would be short-lived. Not because of its failure

[1] But see footnote, p. 554.

to substantiate its claims as a narcotic, nor because it had proved fatal in the hands of physicians, but because an alcohol habit had been developed in some of the population. If one considers the few sporadic cases in which sulphonal or cocaine, for example, has given rise to a habit, and the discredit into which it has fallen in consequence, and compares the cases of disaster from alcohol met with every day, one cannot but feel that the drugs have been weighed in very unequal scales, and that any one who discards cocaine—undoubtedly a drug of great value—must, to be consistent, condemn the use of alcohol. This seems to me to be the ground on which we must take our stand. Alcohol is a drug which may be useful in therapeutics, although I think it can hardly be considered indispensable, but which has so often given rise to habit that its use must be curtailed to the utmost limit. In some conditions, as in old age and debility, it may be justifiable to neglect its drawbacks, exactly as in some forms of malignant disease the patient may be allowed to contract the morphine habit; but let us at any rate advise it here with eyes open to the risks run, and with the recognition that we are prescribing a drug and not merely a placebo. It may be argued that alcoholism has almost never arisen from the therapeutic use of the drug, and it is true that the responsibility for alcoholism does not rest upon the medical profession in the same way as that for morphinism or cocainism. But the public are justified in regarding alcohol not as a drug, but as an article of diet, as long as the physicians order it in the casual way which is familiar to all of us. How often is alcohol not ordered but allowed by the medical man at the suggestion of the patient, and how many physicians allow it, not believing that it will do any good, but assuming that it will do no harm, and even not hesitating to make the statement! The laity can hardly be blamed for ignoring the evidences of danger presented daily in their streets, if their scientific mentors themselves adopt this ambiguous position, and the medical profession cannot complain if they are accused of indifference towards the greatest evil of their country and their age.

THE THEORY OF DIABOLO

By C. V. BOYS, F.R.S.

It would be an interesting subject for a course of lectures or a series of articles to trace the effects of rotation in balls and other objects used in games and in other pursuits. Some of these are fairly obvious, as, for instance, the effect of a spin on a cricket-ball causing it to break after contact with the ground, or the effect of a screw in billiards, where the ball has a rotation about an inclined axis and bounces from the cushion at an angle which by no means obeys the laws of reflection. Here also, in consequence of the rotation the height of the cushion has to be seven-tenths of the diameter of the ball, for in the case of pure rolling the upper part of the ball may be considered to be travelling more quickly than the lower part, and so, if the cushion were only the height of the centre the upper part of the ball would go on and take the rest of the ball with it. Less simple than these are the effects of the air in causing a spinning ball to veer away from the course that it would take if it did not spin. The best known of these is that shown by the flight of a golf-ball, which was first carefully investigated by the late Professor Tait. When the ball is fairly struck by the club, the front face of which slopes somewhat backwards, it is struck at a point below its centre. The rotation imparted is in such a direction as to cause the lower part to move forward most quickly and the front part to move upward. At one time it was supposed, and I believe clearly proved in the armchair in an analogous case, that the front portion moving upward would cause the ball to roll, as it were, upon the air compressed in front of it, and so cause a departure from the natural trajectory, which in the case of the golf-ball would be downwards. As every one knows, the exact reverse is the case, and a proper consideration of the action shows that it should be so, for the air-pressure can be shown, both by theory and by experiment, to be greater below a ball spinning and moving in the directions followed by a golf-ball than above. Professor Tait established

the fact that upward forces due to this cause may be set up which are two or three times as great as the weight of the ball. Another example of this, but less easily followed, is the flight of a spherical bullet from a bent smooth-bore barrel. If such a barrel is curved in a horizontal plane so as to be suitable, according to the story of our childhood, for shooting any one round a haystack, the bullet, far from continuing the curve which it was compelled to follow in the barrel, acquires therein a spin, owing to its rolling along on the concave side, and this spin produces a curvature when free opposite in kind to that of the barrel that gave the rotation. Such a curved flight of a ball is well known in games; the light ball of lawn-tennis when well cut follows a markedly curved course, and, best of all, the child's india-rubber air-ball or balloon when cut by a sweeping stroke of the hand curves rapidly upwards in its flight and provides the material for an excellent and violent indoor winter game.

Mysterious as some of these air-effects may be, they are wholly eclipsed by the queer and apparently semi-contradictory effects of the rotation of a body which are noticed when anything is done to twist the axis of rotation into some other direction. If a grown-up and otherwise well-educated man had never seen a top spin, and, being familiar with the fact that such a body will not stand up upon its point when not spinning, and with the whole science of statics, were suddenly presented with the phenomenon of a spinning-top it is difficult to realise, familiar as we are with the result from our earliest childhood, how great would be his surprise. The fact that it should stand up at all would seem sufficiently uncanny, but its gentle gyrations round the upright position, more rapid as the rate of spin diminishes, would seem to defy explanation. It is only universal familiarity with the phenomenon that prevents surprise or any anxiety in the majority of people to dissolve the mystery. It would be out of place in an article such as this to prove from the simple laws of motion propounded by Newton that a top should spin as it does, or, more generally, how any spinning body will behave when any forces are applied to it which would, if it were not spinning, move the axis about which it happens to be turning into some different direction. This subject is treated in a charming manner by Professor Perry in his book on *Spinning-Tops* and by Professor Worthington in his *Dynamics of Rotation*,

and with rigid accuracy by Professor Greenhill in his articles in the *Encyclopædia Britannica.* It is sufficient here to state shortly the facts. Take the case of the spinning-top. This, if not spinning, would fall over, the toppling-over effect of gravity being greater as the inclination is greater. When the top is spinning the forces due to gravity are the same as before, tending to drag the axis of spin over and downwards, but in consequence of the spin it has a different effect: the axis does not move downwards but sideways, always at right angles to the direction in which it is urged, and so the top gyrates. Further, the rate of moving sideways is greater as the rate of spin is less. If the point on which the top spins is adjustable so that it may be made to project more or less, or may be withdrawn until it is above the centre of gravity, then as it is fixed nearer to the centre of gravity the toppling effect of gravity will be less and the top will gyrate more slowly. When the point on which it spins is at the centre of gravity the toppling effect of gravity is destroyed, and so it ceases to gyrate, and when the point is raised higher still gravity tends to topple no more, but to set it upright: it then gyrates the other way. When gravity acts so as to make it fall it gyrates in the same direction as it spins; when gravity acts so as to set it upright it gyrates in the opposite direction. An example of a slow gyration of this sort is presented by the earth, which would, if it were spherical, maintain the direction of its axis of rotation indefinitely. Any star in the line of this axis would be for all time the pole star. Both the sun and moon in their attraction upon the "equatorial protuberance," or excess of matter outside the sphere, act in such a manner as to drag it towards the plane of the ecliptic, or the earth's orbit round the sun. If this is looked upon as a level, then the sun and moon act together so as to set the top upright. The gyrations then are in the opposite direction to the spin, which is also the direction of revolution round the sun, and so the "equinoxes precess." The pole of the earth describes a circle round the pole of the ecliptic once in about twenty-six thousand years.

When a spinning body of other shape than a ball is projected through the air, the effects of the air upon the direction of the axis of spin, and hence on the motion of the body, give rise to numerous interesting problems. For instance, a disc spun and thrown by the right hand edgeways turns so that the right side

of it rises and it veers to the left; on the other hand, a boomerang started with the same motion rises and comes back again. An elongated bullet neither follows the trajectory, like an arrow, nor maintains the direction of its axis, but conically screws itself round a line slightly above the trajectory. Whenever a spinning body is projected through the air which is in any respect different in its conditions from other cases which have been investigated, a new problem is almost certain to be found, and it is not safe to jump to conclusions.

In the case of the diabolo spool there are really no difficulties, because the air-effects are barely noticeable, and they are of the simple kind observed with golf-balls, tending to deflect the spool to the right as it falls if it is spinning rapidly with a right-hand spin. Ordinarily, in the draughty and eddying enclosures called gardens attached to houses in London, this deviation from a straight fall is not easy to detect, and it certainly is of no importance in the game. If, however, the spool were much lighter, and were ribbed or roughened like a golf-ball, the air-effect would be increased.

With an ordinary spool, the form of which it is unnecessary to define, the centre of gravity is above the string support. It is therefore unstable, and on whichever side it happens to incline, on that side, if not spinning, it will fall. Gravity acts in such a manner as to topple the axis of spin over towards a vertical direction. With the usual right-hand spin the hands are moved in such manner that the string is jerked tight when the right hand is rising, and is loose when it is falling, and the spool gets its support mainly while the string under it is moving from left to right. The upper part, therefore, moves from right to left. In order to correct the level of the axis, when for any reason this ceases to be level, it is necessary to apply forces twisting it not in the desired direction, but in a direction at right angles thereto. Any child will tell you to put the left hand forward if the far end is drooping. Putting the left hand forward means the application of a twist on the axis, tending to turn the far end to the right. This may be proved in a moment by placing the spool on the ground with the string under it and then gradually lifting it with the left hand forward. It will then, not being in a condition of spin, immediately turn so that the far end moves to the right. If the left hand is put forward when the spool is spinning, the effect of the tendency to twist

to the right is a movement in a direction at right angles to the tendency, and the far end rises. There are two directions at right angles to this tendency, one upward and one downward. It is puzzling sometimes to know which right angle will be followed. In the present case it is easy to tell by reference to the known movement of a top. Consider the axis of the spool to be the axis of the top and the far end to be the support of the top, or point on which it is spinning in an anti-clockwise direction, the direction of gravity being supposed for the moment away from you. The action of the string tending to turn the far end to the right or the near end to the left corresponds to the action of gravity on the top when it is leaning to the left, tending to make it fall more to the left. It does not do so, but moves sideways in the direction of the spin, *i.e.* actually towards the earth; or, in other words, the other end, or far end, is raised. If the spin is left-handed of course the result is reversed, and so it is a pity when learning and acquiring the habit to base it upon a consideration which must be reversed when the direction of spin is reversed. The better instruction to follow is to jerk the business hand toward the high side—it being understood, of course, that the business hand is the one which, by its upward jerk, imparts the spin. With such a rule as the early guide the instinct, which is quicker than the recollection and application of any rule, is from the first directed aright, and no conscious effort of reversal is needed whether the direction of spin is right or left handed or the near or the far end is falling.

In order not to be tied to the crab-like method of playing sideways, which is so often seen, it is well to practise playing with a right or left spin indifferently. If playing alone, the change may be brought about by moving round to the side of the spool which is moving upwards and catching the spool on the stick held by the passive hand, then in running the spool down on to the string it will be found to be reversed in direction as seen by the player, but not as regards the points of the compass. This catching on the passive stick is more easily effected, at first, at any rate, by catching on the active stick first and then catching it on the passive stick. The direction of spin may also be reversed by throwing the spool up and turning half round before catching it on the string. Quite a moderate amount of practice, reversing every time by one or

other method, makes the direction of spin a matter of perfect indifference.

I have already referred to the fact that it is necessary for the player to make a half-turn if he would face the spool between every reversal. This is merely another way of saying that the spool maintains its direction in space—that is, it does so if it is perfectly balanced. It is impossible in that case, and provided that it is kept level, to get the spool to veer round to any appreciable extent. If the disturbances were a good deal less than they are, it would in this country appear to follow the sun, but at the reduced rate of nearly 12° per hour, in consequence of the rotation of the earth. Though such accuracy is beyond practical attainment, the persistence of direction is very marked. If while spinning the diabolo a person walks round the garden, he will soon find he is getting his arms involved with one another, as the spool will not turn and the sticks must not either. Or if while travelling in the railway along a curve a passenger is spinning a diabolo and maintaining it level, the apparent turning of the spool will indicate the actual turning of the carriage in the opposite direction. A good place to try this is in the "Bakerloo" tube where it enters the Regent's Park in its northward journey, or in the Hampstead tube in the Euston district.

I have insisted upon the necessity of keeping the spool level when making this experiment. Suppose, for instance, that the far end is down a little and that the usual right-hand spin is being applied, then, as the far end is down to a certain extent, the centre of gravity, instead of being above the string, is on the far side of this position, and gravity tends to topple the spool over on the far side—*i.e.* to turn the spinning axis so that the far end moves downwards. Just as the tendency of the string support to turn the far end to the right makes it actually rise, as already explained, so this tendency of gravity to make the far end move downwards causes it, in consequence of its rotation, to go sideways, and the particular sideways in this case is to the right. If, then, a player desires to work the spool round he has merely, by thrusting one hand forward, to make one end dip somewhat, and then to keep spinning it in that position, when it will veer round—more quickly if the spin is slow—and then, when it has the required direction, to bring the low end up again by drawing the same hand towards himself. It does not matter whether the spin is right or left handed; if the right hand

is put forward to cause one end to dip, the spool will then veer to the right, and *vice versa*, for the end that dips is reversed with a reversed direction of spin, and the action of the reversed tendency to fall, combined with the reversal of spin, gives the same direction of veering. This process was described by a speaker at the Physical Society at a recent meeting where I was showing a peculiar spool, to which I shall next refer.

An ordinary fly-wheel or a disc is twice as effective as a fly-wheel if it is mounted to spin in its own plane, as it would be if it were made to spin on one diameter as an axis. Its moment of inertia is said to be twice as great when spinning as it does in practice as it would be if made to spin about a transverse axis. On the other hand, a diabolo spool or an elongated bullet is less effective as a fly-wheel when spinning about its axis of rotational symmetry. In these cases the moment of inertia is a minimum, while in the former it was a maximum when spinning in the usual manner. Anything, whatever shape it may have, must have some direction about which the moment of inertia is a maximum or a minimum, and it may have a single transverse axis about which it is correspondingly a minimum or a maximum.

If any body is set spinning about any axis and then liberated, it will continue to spin about that axis and resist disturbance only if the axis of spin is one of maximum or minimum moment of inertia. If the body were spun about any inclined axis and liberated, then, according to the position in the body of the inclined axis and the relative values of the maximum and minimum moments of inertia, the axis about which it thereafter is momentarily spinning will move within the body according to one curve and in space according to another, for which an explanation must be sought in Maxwell's Collected Works, vol. i. p. 248. If, on the other hand, the spinning body were a uniform sphere, in which the moments of inertia about all diametrical axes are alike, it would have no tendency to move the axis of spin in any particular manner within itself, and any disturbance would set this axis wandering in the sphere, or, as Maxwell put it, the sphere has no dynamical backbone.

It is not necessary in order that a thing should have equal moments of inertia in all directions that it should be spherical in shape. A long round thing has a minimum moment of inertia

about its axis of symmetry, while a flat round thing has a maximum moment of inertia about this axis. A bullet or an ordinary diabolo spool is an instance of the former, while a fly-wheel or a disc is an instance of the latter. A diabolo spool need not have the usual angle of about 70°, it may be made longer or wider. As it is made wider the moments of inertia in the two directions become gradually more alike, and if it were made wide enough it would correspond in this sense to a fly-wheel, and the respective values would be inverted. There must be, therefore, some intermediate width or angle of cone which makes the moments of inertia in all directions the same, so that dynamically it is the same as a sphere.

It is easy to prove that in the case of a thin hollow double cone, with the ends open and joined point to point, the proportion which gives the spherical characteristic is reached when the angle of the cone is nearly 110°, or when the tangent of the semi-vertical angle is $\sqrt{2}$. All matter added to such an ideal skeleton, without it equatorially makes the axis of rotational symmetry an axis of maximum moment of inertia, all added beyond in the direction of the axis makes this a minimum. A judicious addition of matter without and beyond leaves the double cone dynamically the same as a sphere. If, then, a spool is made of this angle, and of such a thickness as to give a convenient neck for the string by addition of matter without the ideal cone, and by the addition of about the same amount beyond the ideal cone, the resulting spool will be dynamically very nearly a sphere. It is best to make it with an axial hole and with a very slight preponderance of matter without the ideal cone. The moment of inertia about the axis of spin is then just a maximum, and the spool spins perfectly. A number of sticks may then be made of different lengths and thrust centrally, one at a time, into the hole. If any one of these is so exactly chosen in length as to make the moments of inertia in all directions the same, then spinning becomes impossible for the reasons given. In order to ascertain if any stick is too long or too short it is merely necessary to suspend the combination from a torsion wire so as to oscillate about the axis of rotational symmetry and about a transverse axis successively. Then if the time of oscillation about the former is the greater, the stick is too short, and *vice versa*. In order to make spinning really hopeless the time of oscillation should not differ by anything

like so much as 1 per cent., but when equality to this extent is reached the spool becomes sufficiently unmanageable.

When a stick has been properly adjusted the equality fails if the stick is not centrally placed, and the spool can be spun again quite easily. Now, however, being out of balance, the heavy end in tending to fall actually goes sideways, and more quickly so at starting, when the spinning is slow. With a right-hand spin the heavy end, whichever way it is pointing, veers to the right. This may, of course, be equally well shown with any spool which is unbalanced, or which is made so by attaching a nail or a lump of wax to one end. A stick too short to give the spherical property when centrally placed may, nevertheless, do this when pushed out of centre, and then, though the combination will spin perfectly in the first position it is impossible in the second.

It might be thought that the ball in the game cup-and-ball, which at least is a sphere in fact, should not maintain its axis when spun with a view of being caught on the point. But here there are two answers. The first is that though outwardly a sphere the axial hole made for the point to enter destroys its spherical properties. This may be the case to the extent of an inequality in the moments of inertia of perhaps as much as 5 per cent., and this is quite enough to give stability. I have, however, turned a groove in the equator of a well-made ball of this kind to such an extent as to bring the moments of inertia the same, at least to a small fraction of 1 per cent. I was rather surprised to find that I caught this sophisticated ball the first time I tried it. The case, however, is not parallel with the diabolo spool in this respect. While the tweaking of the string on the spool is certain not to be exactly symmetrical and free from disturbing influences, the axial string from which the ball is suspended lifts it when spinning with a pull which must be as truly axial as the turned work is round, and so the disturbance, if any, must be so slight that the ball, in the short time that it is free, has no time to take up an appreciably different position before it is caught. All the time that it is on the string it is held true, while, on the other hand, the spool is only supported and tweaked by the string a very small fraction of the whole time.

Of all the appliances in the class-room for illustrating the precessional properties of rotating bodies I do not know one

which is so inexpensive, simple, and handy as the now popular diabolo. It is whispered that mathematical professors do not always illustrate what they wish very successfully when using gyrostats and Maxwell and other tops. The diabolo seems to have been invented for their special benefit. A complete and proper demonstration of the points described above, and of many others, no doubt, would add enormously to the joy of the class. If at any time the spool should prove refractory the expositor could fall back upon the convenient formula $\tan \theta = \sqrt{2}$, which in time might be contracted to tan, and would so serve the double purpose of an explanation and a harmless but comforting expletive. As a game I do not at all feel inclined to agree with the view that it is not worth while, that it is silly, that it is a mere passing craze. It may, and no doubt will, go out of fashion as quickly as it came in, if indeed it has not already done so, but that is not the fault of the game but of society, who equally threw over cycling before the motor car had destroyed that invigorating pursuit.

SYNTHETICAL DRUGS

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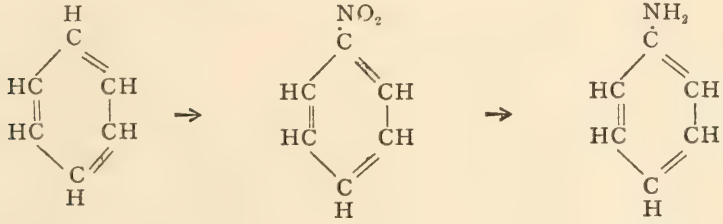
The medicaments falling into the category of synthetical drugs are those which are built up by chemical means from simpler carbon compounds, and not extracted ready-formed from products of the vital activities of plants or animals. In this article it is intended to discuss in simple terms the chemical nature of a typical selection of these therapeutic agents, the trivial or commercial names of which are often household terms.

In 1906 chemists from all parts of the world gathered together in England to celebrate the jubilee of the coal-tar industry, the fiftieth anniversary of the discovery of the colouring matter, mauveine, by the late Sir William Perkin, and 1906 may also be regarded as the jubilee year of the synthetical drugs, for it was in an attempt to synthesise from aniline the valuable alkaloid, quinine, that Perkin discovered mauveine, his researches on aniline being the pioneers of other investigations which led to the employment of this remarkable base, aniline, in the production of compounds of therapeutic value. It is therefore, at the outset, necessary to consider, even though very briefly, the chemistry of aniline and its parent hydrocarbon, benzene. The latter substance, discovered by Faraday in 1825, is the chief constituent of the volatile oil obtained on distilling ordinary coal tar. Chemical analysis shows that the compound consists of twelve parts of carbon united with one part of hydrogen or, in the language of the atomic theory, one atom of carbon combined with one atom of hydrogen. Furthermore, a consideration of its vapour density and other physical properties indicates that a molecule of this hydrocarbon—that is, its smallest conceivable part—is somewhat complex and contains no less than six of these pairs of atoms. A general survey of the compounds of carbon shows that this element possesses in a marked degree the property of accumu-

lating in the molecules of these substances. In certain organic compounds the carbon atoms are arranged in chains which are either straight or branching. If we consider one of these chains having six carbon atoms, and if we suppose further that the chain is coiled so that the ends meet like a snake with its tail in its mouth, we then get a representation of the carbon backbone of the benzene molecule. To each of these carbon vertebræ one of the hydrogen atoms is attached; and now to give the finishing touch to our benzene ring we must consider what is the usual habit of combination of carbon in the many substances in which it is present. Of the thousands of carbon compounds known there are scarcely any which furnish exceptions to the general rule that this element is quadrivalent, or in other words that its atom has four bonds or valencies with which to attach itself to other atoms.

The following graphical formula I. for benzene indicates one of several ways in which this condition is satisfied, this particular mode of representation being due to Kekulé:



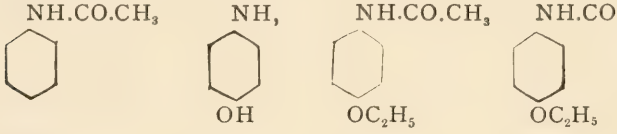
I. II. III.

The double linkings represent points of great reactivity in the molecule, and their presence exerts a very profound influence on the chemical properties of benzene and its derivatives. It is, moreover, largely owing to these double linkings that benzene derivatives are so frequently of therapeutic importance. The physiological action of benzene itself is, however, only slight, the compound having merely the depressing hypnotic effect characteristic of the hydrocarbons in general.

Antipyretics

Aniline (formula III.) is derived from benzene by first treating the hydrocarbon with nitric acid whereby nitrobenzene (formula II.) is produced and then replacing the oxygen atoms in the latter compound by two hydrogen atoms. This process is

called reduction, and is carried out very simply on a large scale by heating the nitrobenzene with iron filings suspended in slightly acidified water. Aniline resembles ammonia in some of its properties, for it is a base capable of yielding well crystallised salts such as aniline hydrochloride and sulphate. Both the base and its salts have a marked physiological action, and in fact they are powerful poisons. These substances have a beneficial effect in lowering the temperature and subduing pain, but on the other hand they have a very deleterious action on the red corpuscles of the blood, bringing about a destruction of the hæmoglobin. Aniline poisoning is characterised by the blue appearance of lips and nails, failure of respiration, giddiness, coma, and finally death. These acute symptoms are, however, considerably diminished by converting aniline into its acetyl derivative, acetanilide, a substance which has been employed as an antipyretic under the name of *antifebrin*[1] (formula IV.). This compound is readily prepared by heating together aniline and glacial acetic acid: $C_6H_5NH_2$, $CH_3 . CO_2H - H_2O = C_6H_5 . NH . CO . CH_3$.

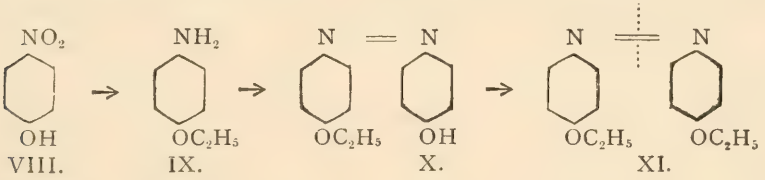


IV. V. VI. VII.

It should, however, be borne in mind that the acetyl group $CO . CH_3$ is readily removed within the tissues either by hydrolysis or oxidation, so that aniline is regenerated, and its poisonous effect is produced only in a less acute form than when the base itself is administered. The continued exhibition of antifebrin is to be deprecated as likely in the long run to produce aniline poisoning. It has been found that aniline is converted in the system into para-aminophenol (formula V.), which is then eliminated in combination either with sulphuric acid or glycuronic acid $COH . [CH . OH]_4 . CO_2H$. This action of the organism in converting aniline into the less poisonous para-aminophenol has been taken into account in the production of the antipyretics of the phenacetin series.

[1] The full graphical representation of the benzene ring or nucleus in formulæ I. to III. has now been simplified to the hexagon represented in formulæ IV., V., etc. It will be seen that this benzene nucleus is present in the majority of the synthetical drugs discussed in this article.

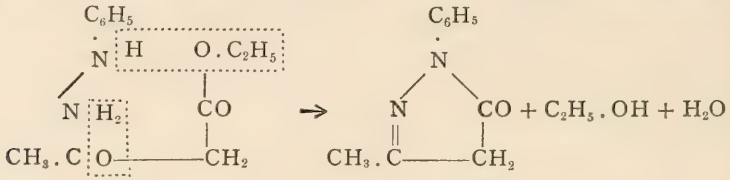
Phenacetin itself (formula VI.) is a febrifuge and an analgesic which is conveniently prepared by the following series of operations: Para-nitrophenol (VIII.) obtained as one of the products of the action of nitric acid on phenol (carbolic acid) is converted by treatment with ethyl sulphate (ethylation) into nitrophenetole $NO_2.C_6H_4.O.C_2H_5$, and this substance is reduced to phenetidine (IX.). This base when treated in succes-



sion with nitrous acid and an alkaline solution of phenol yields the complex compound (X), which is then ethylated to form the substance XI. It will now be noticed that the product XI. is symmetrical about the dotted line, and when it is reduced with tin and hydrochloric acid it splits into two parts at this point, each half taking up two hydrogen atoms and giving rise to a molecule of phenetidine (IX.). One molecule of phenetidine is made to undergo the series of changes represented by X. and XI., while the other molecule is acetylated and thus converted into phenacetin (VII.). This mode of procedure is adopted because of the difficulty of preparing pure paranitrophenol, and in this way an initially small amount of paranitrophenol can be made to produce a large quantity of phenacetin. This drug is somewhat sparingly soluble in cold water, but when the acetyl group is replaced by the lactyl group $CO.CH(OH).CH_3$ derived from lactic acid a more soluble compound is produced to which the name *lactophenin* (formula VII.) is given. This substance has an antineuralgic action; its lactyl group is more readily split off than the acetyl group of phenacetin, and this change occurs under the influence of the acid gastric juices, whereas phenacetin, *methacetin* $NH(CO.CH_3).C_6H_4.OCH_3$, *triphenin*, and other substances of this series are hydrolysed only by the alkaline juices of the intestine.

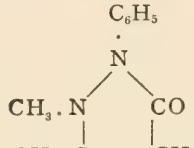
Antipyrine, one of the most important drugs of this group, was originally discovered by Knorr in 1883 in an investigation on the condensation of phenylhydrazine, $C_6H_5.NH.NH_2$, and ethyl acetoacetate, $CH_3CO.CH_2.CO_2C_2H_5$. These two substances, the former of which is an aniline derivative whilst the

latter may be regarded as a complex substance of the acetic acid series, interact to give rise to a compound containing a new ring in the manner indicated in the following diagram:

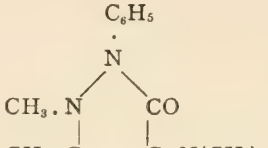


XII.

This product, phenylmethylpyrazolone (XII.), is physiologically inert, but on methylation (treatment with methyl iodide) it gives rise to phenyldimethylpyrazolone (XIII.) or antipyrine.



XIII.



XIV.

This compound is a valuable antipyretic and antineuralgic; it reduces febrile temperatures to the normal, and the subsequent rise of temperature is gradual and unaccompanied by shivering fits. The reduction of temperature is maintained for eight to twenty hours.

Knorr's good fortune in synthesising a therapeutic agent of this order is gauged by the fact that although many other derivatives of the pyrazolone series have been prepared and patented as antipyretics, only one has shown itself to be of anything like the same value as antipyrine. The drug in question is the substance *pyramidon*, which has been placed on the market by the firm of Meister, Lucius & Brüning, who were also the first to prepare Knorr's antipyrine on a manufacturing scale. Pyramidon, dimethylamino-antipyrine (formula XIV.) is prepared by treating antipyrine with nitrous acid, reducing the resulting nitroso-antipyrine to amino-antipyrine and then finally methylating this base to obtain the required compound. This drug is thrice as active as antipyrine; its action begins more gradually and continues for a much longer time. It is prescribed in rheumatism, influenza, and typhoid fever; it forms salts with

the acids of which the most important therapeutically are the salicylate and bicamphorate.

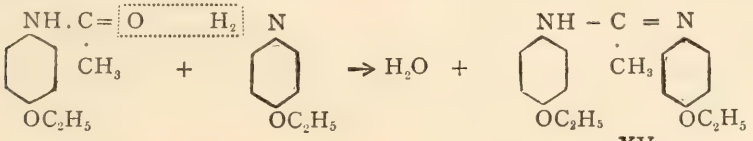
Migrainine, another drug of this series, is antipyrine-caffeine citrate; it is indicated in influenza, neuralgia, and insomnia.

Trigemine (M., L. & B.) is an additive product of pyramidon and butylchloral hydrate $CCl_3 . CH_2 . CH_2 . CH(OH)_2$ which has a marked analgesic action.

Anæsthetics

Closely allied chemically to the phenacetin series are some of the cocaine substitutes employed to produce local anæsthesia.

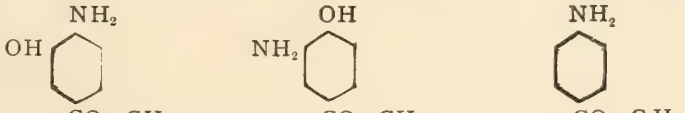
Holocaine is the hydrochloride of the base XV. produced by condensing phenacetin and phenetidine, $C_2H_5O . C_6H_4 . NH_2$. in the presence of phosphorus oxychloride, an agent which serves to remove a molecule of water in the manner indicated below



XV.

As an anæsthetic for operations on the eye its effect is prompt and lasting, and is not accompanied by mydriasis or disturbance of the accommodation of vision. On account of its toxic properties holocaine is not adapted for hypodermic use.

Orthoform (XVI.) and *new orthoform* (XVII.) are the names applied to two isomeric bases the latter of which is generally

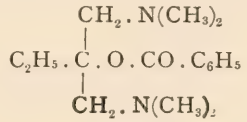


XVI. XVII. XVIII.

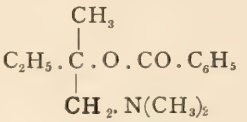
employed at present owing to its lower price. Like cocaine, these compounds render insensitive the nerve-endings and nerve-trunks with which they come into direct contact. This local anæsthesia is, however, not produced through the unbroken skin. A similar substance, *Anæsthesine*, ethyl para-aminobenzoate (XVIII.) is also employed as a local anæsthetic, and is non-irritant and non-toxic. The three foregoing compounds have been placed on the market by Messrs. Meister, Lucius & Brüning.

Novocaine, a derivative of anæsthesine having the formula $NH_2 . C_6H_4 . CO_2 . C_2H_4 . N(C_2H_5)_2$, HCl, is a powerful local non-irritant anæsthetic, seven times less toxic than cocaine, but somewhat transient in its effects.

Alypine, a local anæsthetic recently put forward by the Bayer Company, is the hydrochloride of tetramethyldiaminodimethyl-ethylcarbinyl benzoate (XIX.).



XIX.



XX.

This drug has the useful properties of cocaine without its disadvantages, as even in large doses it does not injuriously affect the heart or respiration, and moreover it does not produce mydriasis.

Stovaine is the hydrochloride of a similar base (XX.); it is produced in the so-called Grignard reaction by the interaction of magnesium ethyl bromide and dimethylamino-acetone followed by benzoylation of the product.

Hypnotics

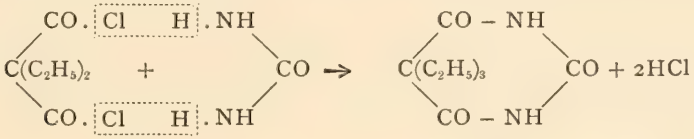
It has already been pointed out that the hydrocarbons themselves have slight hypnotic properties, which, however, become more pronounced when hydroxyl (OH) is introduced into the molecule. This increase in physiological activity is not, however, due to any narcotic action of hydroxyl, which on the contrary has a stimulating tendency. The opposing tendencies of the hydrocarbon and hydroxyl groups are illustrated by the well-known physiological action of ethyl alcohol. Morphine, again, owes its therapeutic action to the presence in its molecule of two hydroxyls, for when these are replaced by methoxyl or ethoxyl the narcotic properties of the alkaloid disappear.

In this connection the hydroxyl must be regarded as an unsaturated group owing to the presence of bivalent oxygen, and the physiological function of these unsaturated groups (hydroxyl, carbonyl, CO, and the doubly and trebly linked carbon atoms $\diagdown\!\!\diagup C=C\diagdown\!\!\diagup$ and $-C\equiv C-$) is to furnish points of attachment between the drug and the reacting compounds of the protoplasm.

The synthetical hypnotics fall into three groups: (1) those containing halogens; (2) those containing alkyl groups and particularly the ethyl group; (3) those containing aldehydic or ketonic groups. Some hypnotics owe their soporific properties to a combination of these characteristics.

Isopral (trichloro*iso*propyl alcohol) is an example of an alcohol containing chlorine, recommended by the Bayer Company as a substitute for chloral hydrate. Isopral is more efficient than chloral and is freer from the depressing effects of the latter. Moreover, it is devoid of any cumulative action or unpleasant after-effects.

Diethylbarbituric acid (XXI), also known as *veronal*, may be regarded as an example of a hypnotic containing alkyl groups. It may be produced by condensing urea (carbamide) with either diethylmalonyl chloride or ethyl diethylmalonate, and many other methods of preparation are being patented even at the present time. Veronal is a colourless inodorous crystalline

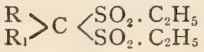


XXI.

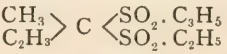
powder melting at 191°C, and dissolving in 12 parts of boiling and in 145 parts of cold water. It is a very satisfactory hypnotic and sedative, rapid in its action and free from untoward sequelæ; it has no disturbing effect on the heart or respiration. Fischer and Mering, who discovered veronal, have since suggested the employment of dipropylbarbituric acid under the name of *proponal*. This substance is also very rapid in its action, doses of 0·2 gram inducing sleep in from fifteen to forty minutes.

Hedonal is a compound of comparatively simple structure $\begin{matrix}CH_3\\C_3H_7\end{matrix}\!\!>\!CH\,.\,O\,.\,CO\,.\,NH_2$ which is advocated by the Bayer Company as a safe soporific. Experiments have shown that this compound is completely oxidised in the system to water and carbonic acid, and it is accordingly quite devoid of any cumulative action. It is indicated in cases of sleeplessness due to mental strain or occurring in the course of neurasthenia or hysteria. When a prolonged use of hypnotics is required it serves as a useful alternative to the other soporifics.

There is an interesting class of hypnotics containing sulphur which illustrate the influence of the ethyl group in the development of the soporific effect. They are produced by the condensation of ethyl mercaptan, $C_2H_5.SH$, with a ketone, $RR^1:C:O$, whereby a mercaptol, $RR^1:C(S.C_2H_5)_2$, is produced, which is then oxidised to a disulphone XXII.



XXII.

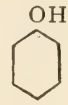


XXIII.

When acetone $(CH_3)_2C:O$ is employed in the condensation, *sulphonal* $(CH_3)_2C(SO_2.C_2H_5)_2$ is ultimately obtained; when diethyl ketone is used, *tetronal* $(C_2H_5)_2C(SO_2.C_2H_5)_2$ is the final product, whilst methyl ethyl ketone leads to the production of *trional* (Bayer). The hypnotic action increases with the number of ethyl groups, tetronal having the strongest narcotic effect. Trional, the intermediate member of the series, is, however, most often employed.

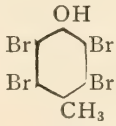
Antiseptics and Astringents

In considering the febrifuges, aniline was taken as the starting-point, and, in a discussion of antiseptics, phenol (carbolic acid, XXIV.) may be regarded as the prototype.

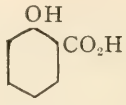


XXIV.

XXV.



XXVI.



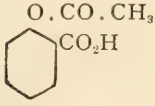
XXVII.

Phenol was, in fact, the first antiseptic recommended in surgical practice when it was employed in the original method of operation introduced by Lister. Although free from the destructive action exerted by aniline on the red corpuscles, phenol is a powerful irritant, and can only be administered internally in very small doses; in larger amounts it has a paralysing effect on the motor nerve-endings. The introduction of a methyl group into the nucleus as in para-cresol (XXV.) brings about a diminution in the poisonous character of phenol and at the same time increases the germicidal power of the substance. On this account the isomeric cresols (para-, meta-, and ortho-) are extensively used in disinfectants of the *lysol* type. The further substitution of halogen atoms for the

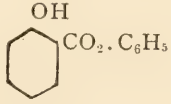
hydrogen atoms of the benzene nucleus also greatly increases the germicidal efficacy of phenol and the cresols. Tetrabromo-para-cresol (XXVI.) and tetrabromo-ortho-cresol are among the most powerful of known germicides.

It has generally been found that the introduction of the acidic groups, carboxyl, CO_2H, and sulphonyl, SO_3H, diminishes very markedly the toxic action of a drug. Benzoic acid, $C_6H_5.CO_2H$, for example, is a substance producing only a very slight physiological effect. When a carboxyl group is introduced into the phenol molecule in a position contiguous to the hydroxyl group *salicylic acid* (XXVII.) is obtained. This product, in the form of its sodium salt, is a very important drug; it has a powerful antiseptic and germicidal effect, is free from the caustic property exhibited by phenol, and it has, moreover, a specific action in acute rheumatism. In its internal effect it greatly resembles quinine, even to the extent of producing a ringing in the ears and transient deafness. When there is toleration of the drug the exhibition of salicylic acid gives excellent results in the treatment of rheumatic troubles, but in certain cases the acid is apt to produce gastric disturbances, and to overcome this unpleasant effect various derivatives of salicylic acid have been put forward.

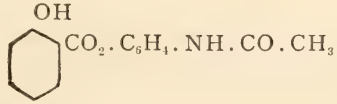
The well-known drug *aspirin*, acetylsalicylic acid (XXVIII.), is a good example of this series.



XXVIII.



XXIX.



XXX.

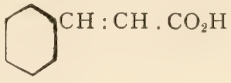
Owing to its insolubility in the gastric juice it is devoid of the irritating action of salicylates on the stomach, but it is decomposed by the alkaline intestinal juices setting free salicylic acid. In order, however, that its action may be entirely beneficial it is important to bear in mind that alkalis of any kind should not be administered immediately after aspirin. A weak acid, such as citric acid, is, on the other hand, a useful adjuvant.

The *salols* are also employed to avoid the ill effects of salicylic acid on the stomach. They pass through this organ unchanged, and are then decomposed by the alkalis of the intestine. In these circumstances *salol* itself (XXIX.) is then

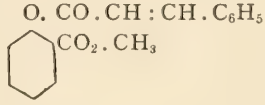
hydrolysed into salicylic acid and phenol. As the latter substance may in the long run produce toxic effects, an improvement on salol has been made by the Bayer Company, who have brought forward the product acetyl-para-aminosalol (XXX.), or *salophen*. This substance, like salol, is insoluble in the gastric juice, but when hydrolysed in the intestine it furnishes salicylic acid and acetyl-para-aminophenol, an innocuous product like para-aminophenol itself (*see* p. 572), which is eliminated without further change.

Mesotan (Bayer Company), $HO.C_6H_4.CO_2.CH_2.OCH_3$, another drug of this class, is chiefly employed in external applications for the local treatment of rheumatic and gouty affections; it is used as a substitute for oil of wintergreen, and is free from the disagreeable properties of this substance.

Although benzoic acid is a comparatively inert substance, the introduction of a double linking between the carboxyl group, CO_2H, and the benzene nucleus leads to the formation of a more physiologically active compound, namely cinnamic acid (XXXI.).



XXXI.

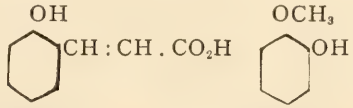


XXXII.

Drs. Jowett and Pyman, of the firm of Burroughs, Wellcome & Co., have endeavoured with success to combine the useful properties of salicylic and cinnamic acids in methyl cinnamyl-salicylate (XXXII.), a compound which has been exhibited in rheumatism and allied conditions with excellent results, being tolerated in cases where aspirin has given rise to dyspeptic symptoms. When given with quinine it prevents the headache and other symptoms of quinism observed in those who are sensitive to this alkaloid. Cinnamic acid in the form of its sodium salt has been recommended in early cases of tuberculosis. When injected intravenously into animals it produces a marked increase in the number of white corpuscles, many of which assume a more active form, indicated by a more granular appearance of their protoplasm. This phenomenon is known as leucocytosis, and this increased activity of the leucocytes is an important factor in the combat incessantly waged by these cells, and more particularly their

active polymorphonuclear forms, against the germs of disease. In Germany a dilute aqueous solution of sodium cinnamate is employed subcutaneously under the name of *hetol*. A solution of this salt in glycerine was suggested for the same purpose by the writer of this article in 1902. An 11 per cent. solution in this solvent is quite stable and free from any tendency to deposit crystals. The high temperature required for its production ensures its sterility, and its viscidity prevents a too rapid mixing of the solution with the blood stream, and thus promotes a more sustained local action. The physiological activity of cinnamic acid is undoubtedly due to its unsaturated ethylene linking, and in this connection it is interesting to notice that an even more unsaturated acid, namely, phenyl-propiolic acid, $C_6H_5 . C \vdots C . CO_2H$, which contains a treble (acetylene) linking, has been used for laryngeal and pulmonary tuberculosis in the form of its sodium salt under the designation of *thermiol*.

An extension of this cinnamate treatment to cases of malignant disease has led to the employment of substances combining the properties of salicylic and cinnamic acids, and the writer has suggested the use of the three isomeric coumaric acids. Of these isomerides the ortho-acid (XXXIII.)



XXXIII. XXXIV. XXXV.

has given the most promising results, both clinically and in germicidal experiments *in vitro*.

The carbolic acid coefficients of germicidal value in respect of *Bacillus typhosus* estimated by the Rideal-Walker method are 6·5 for ortho-coumaric acid, 4·5 for the meta-acid, and 4·0 for the para-acid. These alkali coumarates and *tylmarine*, a preparation of the ortho-acid suitable for internal application, have been prepared by Messrs. Martindale.

Guaiacol, the monomethyl ether of ortho-dihydroxybenzene, a substance either obtained from beechwood tar or produced synthetically from ortho-anisidine, $CH_3O . C_6H_4 . NH_2$, is frequently indicated in tuberculosis, either free or in combination. *Benzosol*, prepared by Messrs. Meister, Lucius & Brüning, is guaiacol benzoate (XXXV.), which is split into guaiacol and

benzoic acid in the intestine. *Duotal* and *creosotal*, prepared by the Bayer Company, are respectively the guaiacol (XXXVA) and creosol carbonates,

$$CO\begin{matrix}O \cdot C_6H_4 \cdot OCH_3 \\ O \cdot C_6H_4 \cdot OCH_3\end{matrix}$$

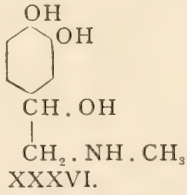
XXXVA.

which exert a favourable action on tuberculous conditions without irritating the stomach.

Synthetical Suprarenine

The synthetical medicaments described above have been employed as substitutes for the naturally occurring drugs, from which they generally differ entirely in chemical structure. The antipyretics of the phenacetin and antipyrin series have been used successfully as quinine substitutes, but nevertheless they do not resemble this alkaloid in chemical constitution. These differences are, moreover, not without their physiological counterpart, for in one respect at least the synthetical febrifuges differ from quinine, and that is in having no specific action in malaria, a malady in which the alkaloid exerts a well-defined beneficial influence. In this section an example of the successful synthesis of a naturally occurring drug will be discussed.

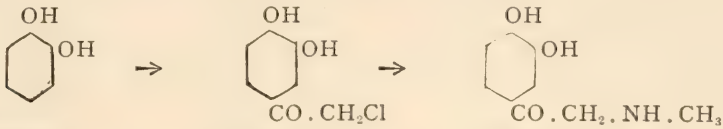
In 1901 Takamine and Aldrich, working independently, succeeded in isolating in a crystalline condition the active principle of the suprarenal capsules. This substance, which exerts an extremely potent influence in raising the blood-pressure, is the most powerful hæmostatic and astringent known. Its constitution was investigated by Von Fürth, Pauly, and Jowett; and in 1904 the last of these investigators indicated three formulæ for the base, stating that he considered that of these the following (XXXVI.) was the most probable:



XXXVI.

A compound having this constitution has since been synthesised by Messrs. Meister, Lucius & Brüning, which appears to have chemical and physiological properties identical with

those of the naturally occurring base. In carrying out this synthesis, catechol (XXXVII.) (ortho-dihydroxybenzene) is treated with chloroacetic acid, $CH_2Cl.CO_2H$,



XXXVII. XXXVIII. XXXIX.

the resulting chloroacetylcatechol (XXXVIII.) is then allowed to interact with methylamine, whereby methylaminoacetylcatechol (XXXIX.) is produced. This substance when reduced is converted into synthetical suprarenine, XXXVI. This base, which is sold in the form of an aqueous solution of its hydrochloride with sodium chloride, can be obtained much more cheaply than the naturally occurring substance. It is, moreover, stable in these circumstances, whereas the natural product undergoes decomposition fairly rapidly. It may be pointed out in passing that this very active drug has received at least three different names—viz. *adrenaline*, *epinephrine*, and *suprarenine*.

Iodoform Substitutes

Space does not admit of more than a brief reference to the synthetical products advocated as substituents for the powerful antiseptic, iodoform, CHI_3.

Isoform (Meister, Lucius & Brüning) is para-iodoxyanisole, $CH_3O.C_6H_4.IO_2$, a substance which is applied either as a dusting powder or in the form of paste; it is prepared from para-anisidine, $CH_3O.C_6H_4.NH_2$, by converting this base successively into its diazo-salt and then into para-iodoanisole, $CH_3O.C_6H_4I$. This product is treated with chlorine, the dichloride hydrolysed into the para-iodosoanisole, $CH_3O.C_6H_4.IO$, and then the last compound heated in steam, whereby equivalent proportions of para-iodoanisole and para-iodoxyanisole are obtained.

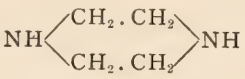
Aristol is an iodo-thymol, whereas *europhen* is isobutyl ortho-cresol iodide; both of these are recommended by the Bayer Company as iodoform substitutes.

Uric Acid Solvents

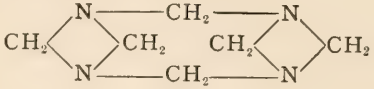
The treatment of gouty disorders with lithium salts has been almost superseded by the application of various synthetical

bases, many of comparatively simple structure, which exercise a marked solvent action on uric acid.

Piperazine, or diethylenediamine (XL.):

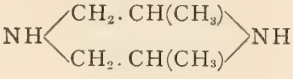


XL.

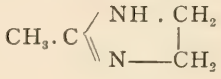


XLI.

is prepared by the interaction of ammonia and ethylene dibromide; it is administered both in the free state and also in the form of its salts, such as the phosphate or tartrate. The internal application of piperazine is followed by an increased elimination of urates from the system, and it is accordingly indicated in cases of chronic gout. Dimethylpiperazine, XLII.



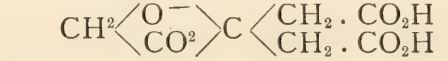
XLII.



XLIII.

(as the bitartrate, *lycetol*), has also been employed in this connection, and so also has *lysidine*, ethylene-ethenyldiamine (XLIII.), a base isomeric with piperazine, which in the form of its bitartrate is stated by Meister, Lucius & Brüning to dissolve eight times more uric acid than piperazine.

Hexamethylenetetramine (XLI.), the base produced by the interaction of formaldehyde and ammonia employed in the form of its salt with anhydromethylenecitric acid



and even the sodium salt of this methylenecitric acid alone, have been employed in this connection, the former under the name of *helmitol*, the latter being termed *citarin*. Hexamethylenetetramine itself has found employment as a diuretic and solvent of uric acid concretions under the name of *urotropine*.

Synthetical Drugs containing Metallic or Metalloidal Elements

There is a growing tendency to employ in therapeutics the organic derivatives of the metals and metalloids in preference to their inorganic compounds, as it not infrequently happens that in this way the element is more readily tolerated, and consequently can be administered with safety in larger doses.

For this reason mercury, copper, and silver salts of the organic acids are frequently employed both internally and externally. *Asterol*, a double salt composed of mercuric phenolsulphonate and ammonium tartrate, is stable in water, and neither precipitates albumin nor attacks metallic surgical instruments. Metallic salts of the organic acids are recommended as antiseptics. *Alumnol* is an aluminium β-naphtholdisulphonate put forward by Meister, Lucius & Brüning. *Nizin*, a zinc salt of sulphanilic acid $(NH_2 . C_6H_4 . SO_3)_2Zn.7H_2O$, is recommended by Messrs. Burroughs, Wellcome & Co. as a non-irritating, non-toxic antiseptic, which even in strong solutions does not coagulate albumin.

Copper cinnamate (*cuprocitral*) has been used in the form of an ointment in ophthalmic work. Strontium cinnamate has been tried in connection with the treatment of tuberculosis already mentioned.

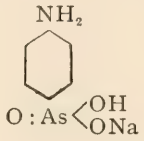
Bismuth salicylate and bismuth cerous salicylate have been employed in intestinal troubles, whilst bismuth subgallate finds employment as a non-irritant antiseptic dusting powder, under the name of *dermatol*.

Arsenic furnishes a good example of an element which is much more readily tolerated in the form of an organic salt. For this purpose sodium dimethylarsinate

$$(CH_3)_2 AsO . ONa, 3H_2O$$

was formerly advocated, as it is less poisonous than Fowler's solution (potassium arsenite). The use of this substance is, however, attended with one disadvantage—namely, the production in the system of malodorous cacodyl derivatives. A much more satisfactory vehicle for the therapeutic application of arsenic has been found in the substance known commercially as *atoxyl*, and which is prepared in a crystallised form by Messrs. Poulenc Frères and also by Messrs. Burroughs, Wellcome & Co. This compound was originally obtained by Béchamp in 1863 by heating aniline arsenate at 190–200° C., whereby a substance was formed which he considered was an anilide of arsenic acid, $C_6H_5 . NHAsO(OH)_2$. On neutralising this substance with sodium hydroxide a soluble crystallisable salt was obtained which was supposed by Béchamp, and more recently by Fourneau (1907), to have the constitution $C_6H_5 . NH . AsO(OH) . ONa$, together with some

water of crystallisation. The properties of the salt do not, however, correspond satisfactorily with this formula, and since the compound has come into use as a drug its constitution has been revised by Ehrlich & Bertheim. Their results, published in the *Berichte der deutschen chemischen Gesellschaft* for July 20th, 1907, show that in reality the substance is a salt of para-aminophenylarsinic acid having the following graphical formula—



and the commercial product generally contains four molecules of water of crystallisation. By analogy with sulphanilic acid, $NH_2 . C_6H_4 . SO_2 . OH$, the free acid has been called arsanilic acid, $NH_2 . C_6H_4 . AsO(OH)_2$, and accordingly atoxyl may be termed sodium arsanilate, $NH_2 . C_6H_4 . AsO(OH)ONa, 4H_2O$. In this substance, the arsenic is very tenaciously held by the organic radicle, and is split off only under the influence of fused potash or by the action of hot hydriodic acid. The strength of the connection between the arsenic and phenyl is probably correlated in some way with the therapeutic action of the salt, for it has been found that atoxyl is forty times less poisonous than Fowler's solution. The salt may be applied either internally or externally; it has been indicated in several maladies, among others in tuberculosis and various skin troubles. Of special interest at the present time are the promising results which have attended the use of atoxyl in cases of sleeping sickness. Although it is as yet too soon to claim any specific action for the drug in this or other diseases, yet it is already evident that in this organic arsenic derivative we have a valuable therapeutic agent.

Although this review of the modern synthetical drugs is unavoidably brief and incomplete, it is hoped that it will serve to throw some light on the chemical nature of these substances many of which are at present in everyday use.

THE ELECTROLYTIC REDUCTION OF ORGANIC SUBSTANCES

By PERCY A. HOUSEMAN, Ph.D. (Würz.), A.I.C.

Organic substances capable of electrolytic reduction may be divided into two classes: (1) easily reducible substances, *i.e.* those which are reduced at any cathode; (2) difficultly reducible substances—those which are reduced only at cathodes possessing a particularly high "super-tension," limited practically to cathodes of lead and mercury. These two classes will be considered separately.

The method, briefly outlined, consists in allowing the hydrogen evolved from the cathode to act upon the organic substance, which is dissolved in a suitable solvent—usually sulphuric acid or aqueous or alcoholic alkali. The substance does not need to be an electrolyte, for the action is a purely chemical reduction by the hydrogen liberated at the cathode. Different chemical agents often lead a reduction in different directions, or arrest the same at different phases; and in the electrolytic process this finds a parallel in the regulation of the course of the reduction by variations in the cathode material—current strength, and, in the case of easily reducible substances, more particularly by the potential,[1] which regulates the pressure under which the ions are discharged from the solution, *i.e.* the energy with which the liberated hydrogen is capable of reacting. A higher potential corresponds in action to the use of a stronger chemical reducing agent.

In a similar way, choice of the size of the electrodes gives the power of regulating the concentration of the discharged ions, *i.e.* the number of ions liberated per unit of cathode surface, this factor also influencing the course of electrolytic reductions.

The earlier work was done on easily reducible substances by

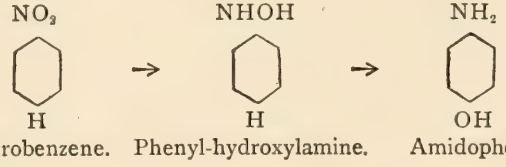
[1] Haber, *Zeitschr. f. Electroc.* 4 (1898), 506; *Zeitschr. f. phys. Chem.* 32 (1900), 193.

Gattermann, Elbs, Haber, Häussermann, Löb, and others. All these investigators paid special attention to the electro-reduction of the nitro- (NO_2) group in aromatic compounds—in particular nitrobenzene—both as a preparative method and also from a purely physical standpoint.

The first experiments on electro-reduction (as well as electro-oxidation) of organic substances were made between 1875 and 1886 by Goppelsroeder,[1] who worked on the production and bleaching of dyestuffs by means of electrolytically produced hydrogen and oxygen. From aniline sulphate by electro-oxidation Goppelsroeder obtained aniline-black, while potassium thiocyanate on electrolytic reduction yielded the dye canarin.

More important, both practically and theoretically, was the work of Gattermann on the electro-reduction of nitrobenzene and its derivatives. The chemical reduction of this substance yields, according to the reducing agent employed, azoxybenzene, azobenzene, hydrazobenzene, aniline, and benzidine. All of these products may also be obtained with the help of the electric current, variations in the conditions of electrolysis corresponding, as noted above, to the use of different chemical reducing agents.[2]

Gattermann,[3] however, and independently Clement and Noyes,[4] succeeded in obtaining an electro-reduction product of nitrobenzene, which all chemical agents had failed to yield, viz. para-amido-phenol. As an intermediate product phenyl-hydroxylamine is formed, subsequently undergoing transformation to amido-phenol, thus:



Nitrobenzene. Phenyl-hydroxylamine. Amidophenol.

Corresponding amidophenols were obtained under similar conditions from other aromatic nitro-compounds, such as nitro-toluene, dinitrobenzenes, etc. When nitrobenzene is reduced

[1] Oesterreich's *Wollen und Leinen Industrie*, Reichenberg, 1885.
[2] See scheme on p. 592.
[3] *Ber. der. deut. chem. Gesell.* 26 (1893), 1849.
[4] *Ibid.* 990.

in alcoholic alkaline solution, the chief products are the azo- and azoxy-compounds, while in acid solution the reduction is carried further, and the hydrazo- and amino-compounds are chiefly formed. This difference in the phase to which nitrobenzene is reduced in alkaline and acid solution, Löb ascribes, in the case of an alkaline solution, to the liberated sodium causing the reduction rather than the nascent hydrogen.[1]

Häussermann[2] was the first to obtain benzidine—

$$NH_2 - C_6H_4 - C_6H_4 - NH_2$$

as an electro-reduction product of nitrobenzene, Löb[3] subsequently obtaining benzidine in excellent yield by reducing first to the azo-phase in alkaline solution, and completing the reduction in dilute sulphuric acid solution. Löb also reduced many derivatives of nitrobenzene, such as the nitrobenzoic acids.

The first attempt to follow these electro-reduction processes quantitatively was made by Elbs,[4] who showed that the reducibility of nitro-compounds diminished as the number of nitro groups is increased. The quantitative investigation of these processes was, however, much more fully worked out by Tafel for difficultly reducible substances, and is described later.

Löb[5] called attention to the effect of different kinds of cathodes on the reduction of nitrobenzene, a factor which is of primary importance with difficultly reducible substances. Thus tin and copper electrodes yielded more aniline, nickel more azoxybenzene. Elbs[6] also showed that under otherwise equal conditions, nitrobenzene was more quickly reduced at a lead cathode yielding more aniline, than at a platinum cathode, at which more amidophenol was produced.

The following scheme shows at a glance the different reduction products which nitrobenzene has yielded, the reduction of this substance, and of its derivatives, by means of the electric

[1] Löb, *Zeitschr. f. Electroc.* 2 (1896), 529.

[2] *Chem.-Ztg.* 17 (129).

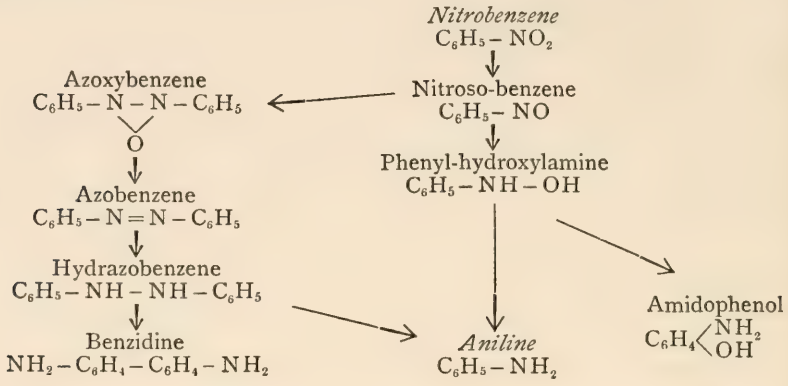
[3] *Zeitschr. f. phys. Chem.* 34 (1900), 641 ; *Zeitschr. f. Electroc.* 7 (1900), 320.

[4] *Journ. f. prak. Chem.* 43 (1891), 39.

[5] *Zeitschr. f. Electroc.* 4, 430 ; Löb and Moore, *Zeit. f. phys. Chem.* 47 (1904), 418.

[6] *Zeitschr. f. Electroc.* 2, 472.

current, having been of considerable theoretical and practical importance.



We turn now to the second class—the electrolytic reduction of *difficultly* reducible substances. This subject is a more recent one. The first such reduction was carried out by Tafel[1] on strychnine in 1898, to be followed in rapid succession by a large number of other compounds, so that the method has become one of great importance not only as a preparative method, but also in view of the many physico-chemical problems involved.

The advantages of the electro-reduction of organic substances —more particularly of difficultly reducible substances—will be considered briefly at the conclusion of the article.

A short description of the method and apparatus employed by Tafel for the quantitative investigation of these reductions must now be given.[2] Experiments must be made on a small scale to see firstly if the substance is capable of being electrolytically reduced at all, and secondly to determine the influence on the time required for the reduction of variations of current concentration,[3] current density,[4] etc. The time required is an important factor, as many of the products obtained are easily decomposable. Such preliminary experiments are made in the closed apparatus shown in fig. 1.

The lead beaker (A) serves as anode. The porous cell (B) separates anode chamber from cathode chamber. The cathode

[1] *Annalen*, 301 (1898), 285.

[2] *Ber. d. deut. chem. Gesell.* 33 (1900), 2209; *Zeitschr. f. phys. Chem.* 34 (1900), 187.

[3] Current concentration = current per litre of cathode liquid.

[4] Current density = current per square centimetre of cathode surface.

chamber is closed by a well-fitting trebly bored rubber stopper, the centre hole of which carries the solid lead cathode (C), while the other holes are fitted with a thermometer (T) and a tube (D) for leading off the evolved hydrogen.

Connected in the same circuit is a second exactly similar apparatus, which contains sulphuric acid only, and *no* organic substance.

The evolved hydrogen from each cell is collected from time to time in a specially constructed pneumatic trough during a

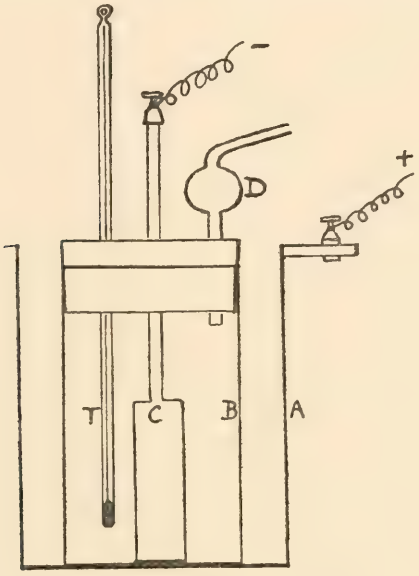


FIG. 1.

period of one minute. The difference in the two volumes (*v-h*) shows how much hydrogen has been used up by the process of reduction, and is a direct measure of the course of the reduction at that moment.

If this difference (*v-h*) is graphically plotted against time, a curve of the velocity of reaction is obtained. Fig. 2 shows a typical curve taken in this case for caffeine. It will be seen that the volume of hydrogen used diminishes regularly with the amount of unreduced substance remaining in the solution. One great advantage which such curves possess is that the area enclosed by the curve and the axes OA·OB is a measure of the total hydrogen used for the reduction. A comparison

between the total hydrogen used and that theoretically required by an equation gives valuable assistance in following the course of the reduction and in knowing what products may be expected. Thus, from the curve in fig. 2 the enclosed area when measured up represents a volume of 2,250 cc. while the equation

$$C_8H_{10}O_2N_4 + 4H = C_8H_{12}ON_4 + H_2O$$

Caffeine Desoxycaffeine

requires (for 10 grams of caffeine) 2,303 cc. hydrogen—the difference between the observed and calculated amounts being well within the limits of experimental error.

It has already been mentioned that the cathode material affects the reduction of aromatic nitro-compounds. With difficultly

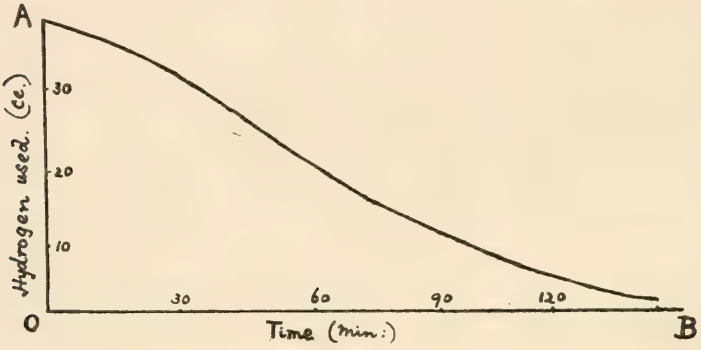


FIG. 2.

reducible substances, such as caffeine and uric acid, a reduction at any other cathode than mercury or lead is seldom possible.

The cause of this important fact is that the hydrogen from a lead cathode is evolved at a higher potential, and therefore possesses greater energy than the hydrogen evolved, say from a platinum cathode. This is intimately connected with the high "super-tension" of lead. Caspari[1] showed that the tension at various cathodes at which gaseous hydrogen visibly escapes differs widely. For lead and mercury this tension is highest—for platinum lowest. The excess of potential over that of a reversibly working hydrogen-oxygen-sulphuric acid element Caspari called the "super-tension" of the metal in question. The following are the values for the "super-tension" of a few metals:

Mercury 0·78 volt.	Lead 0·64.	Copper 0·23.
Silver 0·15.	Gold 0·02.	Platinum 0·005.

[1] Caspari, *Zeitschr. f. phys. Chem.* 30 (1899), 89.

It is this property of rendering difficult the escape of the hydrogen, which lead and mercury possess in such high degree, that allows the reduction of these difficultly reducible organic substances to be accomplished—while at all other cathodes they remain unaffected.

Quantitative experiments such as those already described show that the time required for the reduction is least by using a small current *density* (*i.e.* a large cathode) and as high a current *strength* as is compatible with holding the temperature within the necessary limits. When working on a larger scale, cooling (by means of hollow electrodes) is usually necessary.

One of the most interesting phenomena connected with this subject, and one which is also intimately correlated with "super-tension," is the poisonous influence of traces of foreign metals in the cathode chamber. Tafel[1] has shown that ·004 milligram of platinum per ten square centimetres of cathode surface is sufficient to bring the reduction to a standstill immediately. The other enemies of electro-reduction arranged in order are, after platinum, silver, tin, copper, mercury, zinc, and iron; though none approach platinum in its efficacy in causing the "spontaneous depression" of the reduction.

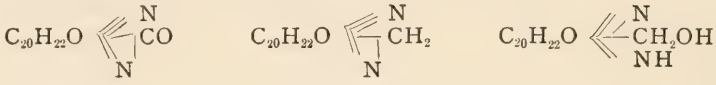
The most obvious explanation of this action is that the platinum is electrolytically precipitated on the surface of the cathode, and that then one is dealing virtually with a platinum cathode, which, as has been already shown, by reason of its low super-tension, *i.e.* the ease with which it allows the hydrogen to escape as gas, does not permit of the reduction being accomplished. Tafel's[2] extensive researches on this problem show that, not only is the amount of platinum present far too minute to form even the thinnest possible skin on the surface of the cathode, but also the action is different on different cathodes, and further, gold, which has almost as low a super-tension as platinum, should have quantitatively almost as great a disturbing effect, whereas gold is not nearly so poisonous to a lead cathode as platinum.

The conclusion is drawn that the platinum must exercise a catalytic influence on the surface of the cathode material. The disturbing action of minute traces of platinum and other metals has been one of the great difficulties in the application of

[1] *Zeitschr. f. phys. Chem.* 34 (1900), 187-228.
[2] Tafel and Emmert, *Ibid.* 52 (1905), 349.

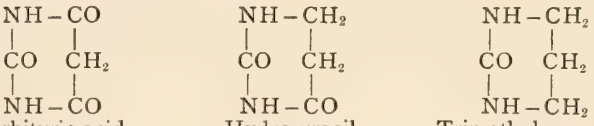
Tafel's electro-reduction process as a preparative method, though the physical researches to which he was thereby forced have revealed much that is theoretically of considerable importance.

The electric current has been most prolific in the preparation of products which cannot be obtained by other reducing agents. A few of these may be mentioned as typical examples: Strychnine,[1] the first of these substances to be submitted to electrolytic reduction, yielded strychnidine and tetrahydro-strychnine, both these substances possessing in a less degree the same physiological action as strychnine.



Strychnine. Strychnidine. Tetra-hydro-strychnine

As an example from the ureides, barbituric acid[2] may be cited, this substance yielding on reduction a mixture of hydro-uracil and trimethylene-urea.



Barbituric acid Hydro-uracil Trimethylene urea

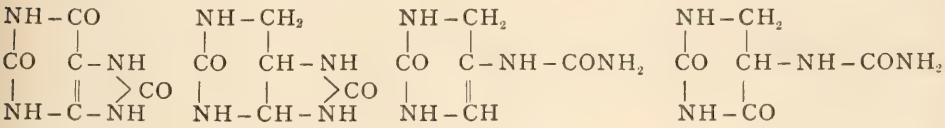
The behaviour of di-ethyl-barbituric acid,[3] which is now being used somewhat extensively as a soporific under the name of Veronal, is very remarkable. Instead of being reduced in a manner analogous to barbituric acid, the hydrogen attacks the urea residue thus :—

Up to the present this is the only observed instance in which the carbonyl (CO) group of the urea chain has been electrolytically reduced.

Of particular interest are the electro-reduction products of uric acid,[4] inasmuch as this physiologically important body has not been directly reduced by any other means, if one leaves out of account the breaking down of the molecule by hydriodic

[1] *Annalen*, 301 (1898), 285.
[2] *Ber. d. deut. chem. Gesell.* 33 (1900), 3383.
[3] Tafel and Thompson, *Ber. d. deut. chem. Gesell.* 40 (1907), in press.
[4] *Ibid.* 34 (1901), 258.

acid. Three substances are obtained by the electrolytic reduction of uric acid—puron, isopuron, and tetra-hydro-uric acid. The manner in which the hydrogen is added on is seen clearly from the following formulæ.



Uric acid Puron Isopuron[1] Tetra-hydro-uric acid

It will be noticed that puron and isopuron are isomeric, *i.e.* they possess the same empirical formula, $C_5H_8O_2N_4$. The former is transformed to the latter by treatment with caustic alkali.

The methyl derivatives of uric acid[2] also yield a series of corresponding methyl derivatives of puron and isopuron. In no case, however, is a substance corresponding to tetra-hydro-uric acid produced.

The slightly higher super-tension of mercury than lead is the cause of some substances being reduced better with a cathode of the former metal than with one of the latter.[3] Examples are acetone and caffeine. In the case of camphor no reduction whatever takes place at a lead cathode, while, with a mercury cathode, borneol is obtained in good yield.

It is to be expected that the electric current will come more and more into use as a preparative method for the reduction of organic substances. By varying the potential one can, as Nernst expresses it, produce pressures whose amount varies between very small fractions of an atmosphere, and many million atmospheres; and this is the reason why the electric current accomplishes the reduction of some substances, such as uric acid, which remain entirely unaffected by the ordinary chemical reducing agents.

The successful clearing away of the many preliminary difficulties leaves the method a well-understood and comparatively simple one, besides which, electro-reduction possesses the further advantage of the absence of other reagents, which usually entail a more or less troublesome process of elimination in the course of reduction by the usual chemical agents.

[1] Tafel and Houseman, *Ber. d. deut. chem. Gesell.* 40 (1907), 3743 (in press). Houseman, *Dissertation*, Würzburg, 1906.

[2] *Ber. d. deut. chem. Gesell.* 34 (1901), 279.

[3] Tafel and Schmitz, *Zeitschr. f. Electroc.* 8 (1902), 280.

DIFFUSION AND ENTROPY OF GASES

By S. H. BURBURY, F.R.S.

1. This subject has been treated by Lord Rayleigh in *Phil. Mag.* January—June 1875, under the title "On the Work that may be gained by the Mixture of Gases," pp. 311, 318, and by Prof. Bryan in his recent work on *Thermodynamics* (Leipzig: Teubner). Each writer's work presents some difficulties, which I propose to consider in the present paper. Rayleigh's argument is based on the fact that hydrogen escapes through fine apertures more rapidly than air, even at greater pressure, enters to supply its place. His conclusion is that "the work that may be done in the mixing of volumes v_1 and v_2 of two different gases is the same as would be gained in the expansion into vacuum of the first gas from volume v_1 to $v_1 + v_2$, together with that which would be gained by the expansion into vacuum of the second gas from volume v_2 to $v_1 + v_2$." It is understood that the gases follow the law of independent pressures, each behaving as a vacuum to the other. The law is thus stated with complete generality, and without qualification as to the nature of the containing materials or otherwise. Bryan states the law in substantially the same form at p. 125 of his work. I therefore call it the Rayleigh-Bryan law.

2. The thing to be proved, as I understand it, is this: that two physically different gases, if separated, can be made to do mechanical work, at the expense, of course, of their heat, in mixing; on the other hand, if they mix by diffusion, no work is done. Therefore by allowing them to mix by diffusion, we lose the opportunity of converting heat into work, *i.e.* we lose the "available energy" which they had by virtue of their separation.

3. Before discussing the arguments in detail, it will be well to calculate the work that can be done in case of two gases, one of which is hydrogen, in a cylinder of volume 2v, separated, as Rayleigh suggests, by a piston porous to the hydrogen, but hypothetically impermeable to the other gas, say oxygen. They

are supposed to be both at the same pressure, p, and the same temperature, and each initially occupying volume v. Also the temperature is maintained constant notwithstanding the conversion of heat into work during expansion of either gas. The piston being fixed, hydrogen escapes through it, until it is of the same density throughout the cylinder, oxygen behaving as a vacuum to it. This being done, the pressure is $\frac{3p}{2}$ on the oxygen side, and $\frac{p}{2}$ on the hydrogen side. The piston being now set free, the oxygen expands, and if its expansion takes place very slowly, the hydrogen, as it can pass through, will be throughout the process at the same pressure on either side of the piston. The work done by expansion of the oxygen is then the same as if the hydrogen were absent, and is

$$\int_0^v \frac{pv}{v+x}\,dx = pv \log 2.$$

It is therefore exactly half the work required by the Rayleigh-Bryan law. At the end of the process the two gases are uniformly mixed throughout the volume 2v of the cylinder. No further work can be obtained from the system while it is in that state. If the piston, instead of being impermeable to oxygen, were permeable by it, only in less degree than by hydrogen, the work obtained would be less—that is, less than half the work required by the law.

4. We must now consider Rayleigh's arguments. They seem designed to show that the separation of mixed gases generally involves the expenditure of work, and that this work may be regained in their mixture. In his first example a mixture of steam and hydrogen under a piston in a cylinder of volume v is compressed, the temperature being maintained constant, until at volume v_1, the saturation point of the steam is reached, and it begins to liquefy, and is all liquefied at volume v_0. I understand Rayleigh to say that at this point all the hydrogen exists as gas between the water and the piston, none being held in solution by the water. The water is then put in a separate vessel, and is evaporated and expanded to its original volume and temperature. The hydrogen also expands to its original volume and temperature. The work gained in expansion is, he says, equal to that spent in compres-

sion, so that in the complete cycle, the whole system being restored to its original state but for the separation of the gases, no work on the whole is done. Does this result support Rayleigh's doctrine? It is true work is spent during the separation, and gained during the subsequent expansion—that is, the gases when separated have available energy. But this is not because they are separated, but because they are compressed, and they would have precisely the same available energy if they were not separated at all, but expanded as a mixture to their original state.

5. In his second example Rayleigh shows how the separation of two gases may in a certain case, and doubtless in other cases, be effected by chemical means.

6. In the third argument (p. 313, etc.), Rayleigh considers the case in which two gases, a heavier and a lighter, say oxygen and hydrogen, are partially separated by the action of gravity in a vertical tube. Suppose them to have arrived at a state of equilibrium, and the partial pressures at the base of the tube are the same as those of the same two gases mixed in a reservoir, so that if the tube communicates with the reservoir at its base no oxygen or hydrogen escapes from or to the reservoir. Rayleigh proves that if the mixture of gases in each element of the tube be separately compressed to the total pressure at the base, and is then brought down to the level of the base, the work spent in the compression exceeds in the case of two gases that gained from gravity in the descent. Were only one gas present, it would be equal to the work gained.

7. In order to make the cycle complete, except that at the end the gases are partially separated, at the beginning uniformly mixed, I will work out the problem independently. As will be seen, I shall obtain Rayleigh's result above stated. I consider two cases:

Case I.—A single gas is at uniform pressure and temperature in a horizontal tube ACB of length S. C is the middle point, and initially the centre of gravity of the gases. I avail myself of the permission given by Rayleigh (p. 318, line 3) to divide the tube into elements of length, and to insert between each pair of successive elements a piston, fixed or movable, to prevent passage of molecules from one element to another, also permission to remove such pistons. Then—

Process (1). Fix the pistons and turn the tube about the end

A into the vertical position. In that we spend work MgAC, if M be the mass of the gas. We need not take into account the mass of the tube.

Process (2). Set the pistons free, then compression ensues towards the base. The centre of gravity falls to C_1. We gain work from gravity MgC_1C, which is all spent in the compression.

Process (3). Again fix the pistons, and turn the tube about A into the horizontal position. In that we gain work $MgAC_1$.

Process (4). Let the gas expand till it reaches its initial uniform density. In that we gain work by the expansion equal to the work spent in compression, that is MgC_1C.

In all we have spent work MgAC in (1) and gained work $MgAC_1$ in (3) and MgC_1C in (4)—that is, we have spent zero work.

8. *Case II.*—Instead of a single gas, let there be in the horizontal tube equal numbers of molecules of oxygen and hydrogen uniformly mixed, then insert and fix the pistons, and perform Process (1) as before. In that we spend work MgAC as before, M being the combined mass of the gases.

Process (2). Set the pistons free, and compression takes place as before. The c g falls to C′, and the work of compression, which is done by gravity, is MgCC′.

Before Process (3) we must now interpolate a new process (2A)—namely, remove the pistons, so that diffusion takes place. The gases assume a new position of equilibrium, in which each behaves as a vacuum to the other.

If R_1 denote the density per unit of volume for oxygen at the base, r_1 its density at height s, and if R_2, r_2 be the corresponding densities of hydrogen, $r_1 = R_1 e^{-2hm_1gs}$, and $r_2 = R_2 e^{-2hm_2gs}$, m_1 being the mass of a molecule of oxygen, m_2 that of hydrogen —that is, oxygen partially replaces hydrogen in the lower, hydrogen replaces oxygen in the upper strata. The centre of gravity falls to C″. Before considering what becomes of the work thus gained MgC′C″, let us perform Processes (3) and (4). Fix the pistons, Process (3), and turn the tube about A into the horizontal position. In that we gain work MgAC″.

Up to this point we have spent work MgAC, and gained MgAC″.

Then Process (4), set free the pistons, and let the gases expand without diffusion till they attain uniform pressure, but not uniform mixture, throughout the tube. The work gained in

that expansion is equal to the work spent by gravity in the compression. If, then, the work gained from gravity in Process 2A, namely MgC″C′, is all spent in compression, there is in the complete cycle zero work spent.

But if, as I think is the case, part only of the work MgC″C′ is spent in compression, and part converted into heat, *i.e.* dissipated (see Raleigh's remarks, pp. 317-8), we have in the whole spent work equivalent to the dissipated energy.

9. Is not the theory this? If we had suitable machinery to act on individual molecules, *e.g.* if we could employ Maxwell's demons for the purpose, we might effect the separation of the oxygen and hydrogen molecules mixed in the horizontal tube without doing any work, no work being *essential* to the process, unless molecules of the same gas appreciably attract or repel each other, which is understood not to be the case. As we have no such machinery, and cannot employ the demons, we have to effect the separation by indirect processes, as in the example given. And these indirect processes generally involve dissipation. Work is spent in the separation of the gases, but the energy is in no sense available. Energy dissipated is unavailable.

Professor Bryan's Argument

10. I come now to Prof. Bryan's argument, which is mainly theoretical. I will give his proof of the law (for there is a logical proof) as I understand it. I begin with his definition of "entropy," the second of p. 58.

(*a*) If the unavailable energy of any system receives any positive or negative increase δQ, the entropy is increased by $\frac{\delta Q}{T_0}$, T_0 being the lowest available temperature. I think we may say, at least by way of example, without affecting the generality of this definition, that δQ is the heat which passes into the refrigerator in the lower isothermal of a Carnot cycle in which the system is the working substance.

(*b*) This being the definition of entropy, it follows that if the entropy increases, the unavailable energy increases. Therefore, since energy is either available or unavailable, if while the entropy increases no energy enters or leaves the system from or to external bodies, the available energy diminishes.

(*c*) The entropy of a system is a function of the physical

state of the system, and cannot change while that state remains unchanged. Therefore, if the system be a gas, at all events if a perfect gas, it may be expressed as a function of the temperature and volume—and, it may be, also a function of the number, n, of molecules in the given volume, say generally it is f(n, T, v).

(*d*) But, if the gas be the working substance in a Carnot cycle, the heat drawn from the reservoir in an isothermal expansion from volume v to volume v + δv is proportional to the pressure, that is, for given v, proportional to n. Therefore, also, the heat δQ, which passes into the refrigerator in the same cycle, is proportional to n. Therefore, if S_n be the entropy of a single gas containing n molecules in volume v, $S_{n'}$ the entropy for the same gas containing n′ molecules in volume v, $\frac{\delta S_n}{\delta S_{n'}} = \frac{n}{n'}$. And since S_n and $S_{n'}$ cannot differ by a constant, $\frac{S_n}{S_{n'}} = \frac{n}{n'}$. That is, $\frac{f(n, T, v)}{f(n', T, v)} = \frac{n}{n'}$ for all values of n and n′. This requires that f (n, T, v) = nφ (T, v), where φ (T, v) denotes some function of T and v. Therefore f (n + n′, T, v) = (n + n′) φ (T, v) = nφ (T, v) + n′φ (T, v), or the entropy of a single gas, in volume v, is the sum of the entropies of all the parts into which it may be conceived as divided, provided that each part is free to move throughout the whole of v, and is not confined by partition to a part of v. (N.B.—This is my own argument, and not Bryan's. It would not necessarily apply to two different gases, because the physical state of each might be affected by the presence of the other.) Bryan, however, proves the same thing for two gases as follows:

(*e*) The entropy of a gas occupying volume v is the same whether it has that volume all to itself, or shares it with another gas at the same temperature and pressure. In other words each gas is in respect of its entropy a vacuum to the other. *Query*, is there any limit to this law as the density increases?

A proof of this is given at p. 124 by the following method, which I understand to be founded on experiment. Given a mixture of two gases in cylinder of volume 2v, each having the same partial pressure ½p, and the mixture having combined pressure p, the mixture is cooled until the gases liquefy, one before the other. The liquids are put in separate vessels,

and evaporated, and heated until each occupies volume 2v, and is at the original temperature of the mixture. It is assumed (1) that the volumes of the liquids are negligible in comparison with their vapours; (2) that the specific heats are constant; (3) that the latent heat of evaporation of either component is unaffected by the presence or absence of the other. On these assumptions Bryan concludes that the process is reversible. Therefore entropy is the same at the end, when each gas has a volume 2v to itself, as at the beginning, when they had one volume 2v in common, *cæteris paribus*.

(*f*) The entropy of a gas in volume v increases, *cæteris paribus*, when v increases. This follows from the definition (*a*). For S denoting entropy, $\delta S = \frac{\delta Q}{T_0}$; therefore $\frac{dS}{dv} = \frac{1}{T_0}\frac{dQ}{dv}$, and $\frac{dQ}{dv}$ is always positive by the Carnot cycle.

11. We may now compare two states of a system: state A, two gases occupying each a volume v, separated by a partition, and each at pressure p, and temperature T; state B, the same two gases mixed in volume 2v, *cæteris paribus*. Each gas has in state A entropy $n\phi(T, v)$, and by (*e*) it has in state B entropy $n\phi(T, 2v)$, which by (*f*) is greater than $n\phi(T,v)$—that is, each has greater entropy, and therefore the system has greater entropy in B than in A. Therefore the system has less available energy in B than in A, or available energy is lost in the process of mixing, no energy passing in that process from or to external bodies.

12. Evidently the amount of available energy that each gas loses in the process of mixing is measured by the entropy that it gains—that is, the difference of entropy between the gas occupying volume v, and the same gas *cæteris paribus* occupying volume 2v—that is, the available energy lost by the process is for each gas the available energy it would lose by expanding into vacuum from volume v to volume 2v, the temperature being constant. The Rayleigh-Bryan law is thus formally and completely proved in the sense of Bryan's definition of available energy, whatever that may be.

13. I note that Bryan's process of separating the gases (p. 124) involves no expenditure of work. If, therefore, the gases when separated have more available energy than when mixed, it is not because work has been spent in their separation which can be regained in their mixture, in which Bryan seems to differ from Rayleigh.

14. The argument (Bryan's) seems to prove too much, if I am right in (*d*) above. For if so, the argument applies equally to two portions of any single gas. Therefore, we could increase the available energy of a single gas by dividing it into two parts by a partition. Even if (*d*) be not accepted, does not the same thing follow from Bryan's proof (*e*) applied to two portions of the same gas? It is true that this process, although it separates two gases having different temperatures of liquefaction, cannot separate two portions of the same gas. But we may separate the two portions, and put them in separate vessels, immediately after or before liquefaction, and then evaporate them separately, till each attains its original temperature and original volume 2v. If the process is reversible for two gases, is it not equally reversible for two portions of the same gas? If so, then two portions of the same gas, each at the same temperature and pressure, mixed in one volume 2v, have more entropy than they would have if they each occupied volume v, and were separated by a partition.

15. Subject to the doubt raised in 14, the argument of arts. 10 and 11 seems logically conclusive, that two separated gases lose available energy, whatever that may mean, when allowed to mix by diffusion, and that the amount of available energy lost is that stated in the Rayleigh-Bryan law.

16. Nevertheless, it does not necessarily follow that the available energy lost is *the practical possibility* of transforming heat into work. For the only definition of available energy which we have used in the argument is that it diminishes with increase of entropy. In fact, if the entropy is a function of T and v, and independent of any conditions, the available energy must be a function of T and v, and independent of any conditions. It does not, therefore, follow that because a system loses available energy in passing from state A to state B, therefore we can actually transform heat into work given the system in state A. It may be that in state A work is *theoretically*, but owing to the external conditions not *practically*, derivable from the system. In Bryan's definition of available energy (p. 43) "work theoretically derivable" must mean "work which under suitable external conditions might be derived." If two separated gases (state A) are each at pressure p, and are surrounded by infinite air at pressure p and at the same temperature as the gases, no part of the heat of either gas can

be transformed into work while the whole system is what it is. We then call upon the experimental philosopher to convert it into something that at present it is not, but without initially altering its entropy. This he can do by substituting for the partition separating the gases a piston porous to one, but not, or not in the same degree, porous to the other. We might say paradoxically that, while the separated gases are separated, the available energy is not available; but when by using the porous piston the separated gases are not separated, the available energy, or some part of it, is available. A dinner is placed before Tantalus, and it is mathematically proved to him that it is an available dinner, but he is unable to eat or drink.

17. There may be other transformations of the system which would admit of work being obtained. One other method has been suggested—namely, a liquid which absorbs one of the two gases, but not the other. By such a liquid we might perhaps reduce one of the two gases to lower pressure than the other, and so render the performance of work possible. But that method might be applied with equal success to two separated portions of a single gas.

18. Bryan uses instead of the porous piston a membrane (p. 125). And he suggests the ideal case of two membranes, one of which is porous to gas (1), but wholly impermeable to gas (2), the other membrane *vice versa*. But should not this ideal combination of gases and membranes be required to prove its own existence before it is used to prove anything else? If Bryan says it does exist, I accept his authority.

19. Another line of argument to prove the Rayleigh-Bryan law, not expressly relied upon by Bryan, is as follows: If any irreversible process takes place in the interior of a system, the unavailable energy of the system, and therefore the entropy, is increased. And the mixture by diffusion of two gases originally separated is stated by Bryan to be an irreversible process. I admit the argument, if the diffusion is an irreversible process. But there is no proof that it is not a periodic process.

20. It is, of course, a familiar experience that two separated gases, each at the same pressure and temperature, if the partition be removed, at once begin to mix—or, let us say, if they are originally mixed in different proportions on the two sides of the partition, at once begin to assume a more uniform mixture. But

that phenomenon is as consistent with the motion being periodic as with its being asymptotic—*i.e.* irreversible. For if periodic, any point in the path may be described in either of two directions, typically the paths may be ABCA, or ACBA. By the way in which we make the experiment, we determine the direction to be that in which the initial motion is towards more uniform mixture, say ABCA, if B denotes the initial, and C a state of more uniform mixture than B. That is because initially the two gases are *at rest* relatively to one another. As an example, suppose a semicircular smooth tube in a vertical plane with its middle point as base, and in it a heavy particle. The particle, if free to move, and placed at rest at a point above the lowest, will begin by moving downwards. But it will oscillate about the lowest point, and will not move irreversibly to the lowest point. The reason why it begins by moving downwards is because it starts *from rest.* For precisely the same reason the two gases, each *at rest relatively to the other*, begin by moving towards the more uniform mixture. But there is no proof that the motion is irreversible.

21. It is true no man has ever observed them to begin to separate. But to make this evidence of the irreversibility, it would be necessary to continue the experiment for a time at least equal to half the period, if the motion be periodic. And not only that, but also to completely protect the system from all disturbances from without during the whole time. Has this ever been done? And as regards external disturbances, can it be done? If practically it cannot be done, then it may be that in any experiment that can practically be performed, the motion will appear to be irreversible, because the external influences prevent it from being periodic. But then they also prevent the argument from being applicable.

22. If the diameters of the molecules were so small that no collisions occurred, the motion must be periodic. Can it be proved that collisions convert it into an irreversible motion?

23. I think we unconsciously derive the idea of the motion being irreversible from Boltzmann's H Theorem, which is supposed to prove that an irreversible motion of a gas is possible, and that, I think—although the weight of authority against me is immense—rests on "a misuse of the theory of probabilities."

We suppose that at an initial instant the co-ordinates and

velocities of the molecules are distributed at haphazard, subject to the conditions (1) that the total kinetic energy is a given constant T, and (2) that Boltzmann's function H has a value greater than its minimum. And we then prove that $\frac{dH}{dt}$ is, under those circumstances, much more likely to be negative than positive. That is true. But the initial values of the variables having been once assumed, their values after any time t are determinate functions of the initial values and of t. The law of probabilities has nothing further to say in the matter, but having fixed the initial values is *functus officio*.

24. The error consists, as I maintain, after the manner that men call heresy, in assuming the law of probabilities to have continuous action, as though an independent haphazard distribution of the variables took place at every instant. If that were the case, it is true that $\frac{dH}{dt}$ would be on an average negative at every instant, and the motion could not be periodic. There are, in fact, at the initial instant a great number, say n, of possible states of the system, and as many possible determinate courses for all subsequent time. By the way in which we make the initial distribution, each of these n states, with its determined course, is as likely to happen as any other. Further, as we are in complete ignorance of the sequence of events in any one of the n courses, it is true that, to our minds subjectively, each state of the system is at every instant as probable as any other. But this ignorance of ours would exist in fact whether the motion be periodic or irreversible. We cannot therefore argue from our ignorance of the courses that the motion is irreversible. For this reason I think the usually accepted proof is illogical.

25. Further, the objection to the H Theorem, first made, I believe, by Loschmidt, that if all the velocities were at any instant reversed, the system would retrace its course, is, to my mind, fatal to any theorem of irreversible motion in a gas whose molecules are such as the kinetic theory assumes, provided that the isolation of the system be complete. Of course, if a fresh haphazard distribution took place at every instant, as the theory requires, the Loschmidt objection would fail altogether, for on reversal of the velocities the system would *not* retrace its course. And any external disturbance,

coming at haphazard, independently of the existing state of the system, effects a new distribution *pro tanto.*

26. I know it is said in defence of the theorem that the reversed motion, though possible, is highly improbable. But if the H theorem be true, Maxwell's law of distribution of the velocities must be assumed to prevail ultimately, or anyway cannot be denied by advocates of the theorem. From which it follows that any course and the reversed course are equally probable. To say that one of the two is the more probable *because it leads to H diminishing* would be a *petitio principii.*

27. If, as I think is the case, the complete protection of two diffusing gases from all external influences continuously for a very long time is impossible, the motion is, as I have said, for that reason irreversible, because the external disturbances are equivalent to a new haphazard distribution. But for that same reason the irreversibility does not necessarily involve increase of entropy, and the whole argument falls to the ground.

28. I have asserted generally that if the molecules of gases are what they are assumed to be in the kinetic theory, no irreversible motion is possible in an isolated system. Very probably it may be necessary to revise our conceptions of a molecule, and Prof. Bryan's work may well be conducive to that end.

THE PRICE OF ANÆSTHESIA

By AUGUSTUS D. WALLER, M.D., F.R.S., LL.D.

The debate that took place a few weeks ago through the columns of *The Times*, between the scientist who finds his public too ignorant to understand him and the public who finds that the scientist talks a learned jargon that is a sign and symptom of his own imperfect knowledge, is one that should not fail to be heeded by any person making bold to say something in the pages of Science Progress. For we are, all of us, in relation to each other's work and thought, very public indeed; the barrier of language is raised not only between scientists and public, but between scientists and scientists, and the public is hardly to be condemned as ignorant if the instructors themselves remain immured from each other, as well as from "the public," in their private apartments of thought and language.

If it be true that nothing new in science is achieved otherwise than by "constantly thinking unto it," it is equally true that "the greatest thing a human soul does in this world is to see something, and *tell* what it saw in a plain way.

I am perhaps rashly challenging an adverse verdict by proclaiming at the outset a standard of excellence that I may hardly hope to reach—that I shall, however, attempt to reach—by telling in a plain way something that I have seen.

Chloroform, the anæsthetic *par excellence*, that has conferred upon mankind the great boon of surgical anæsthesia, is known, or will one day be known, to the vast majority of us by actual personal experience. That is a first reason to enlist our interest. It is one of the most efficient and certain poisons known; its certainty and regularity of action are such that it is systematically used for mercifully getting rid of lost dogs, and an unknown but considerable number of persons annually lose their lives in consequence of chloroform administered for the purpose of producing surgical anæsthesia—"skilfully administered for a necessary surgical operation," to quote words frequently employed by coroners' juries. The number of officially

recorded deaths in England registered as due to anæsthetics during the ten-year periods was:

1866 to 1875	. . . . .	146 deaths.
1876 „ 1885	. . . . .	264 „
1886 „ 1895	. . . . .	533 „
1896 „ 1905	. . . . .	1,269 „

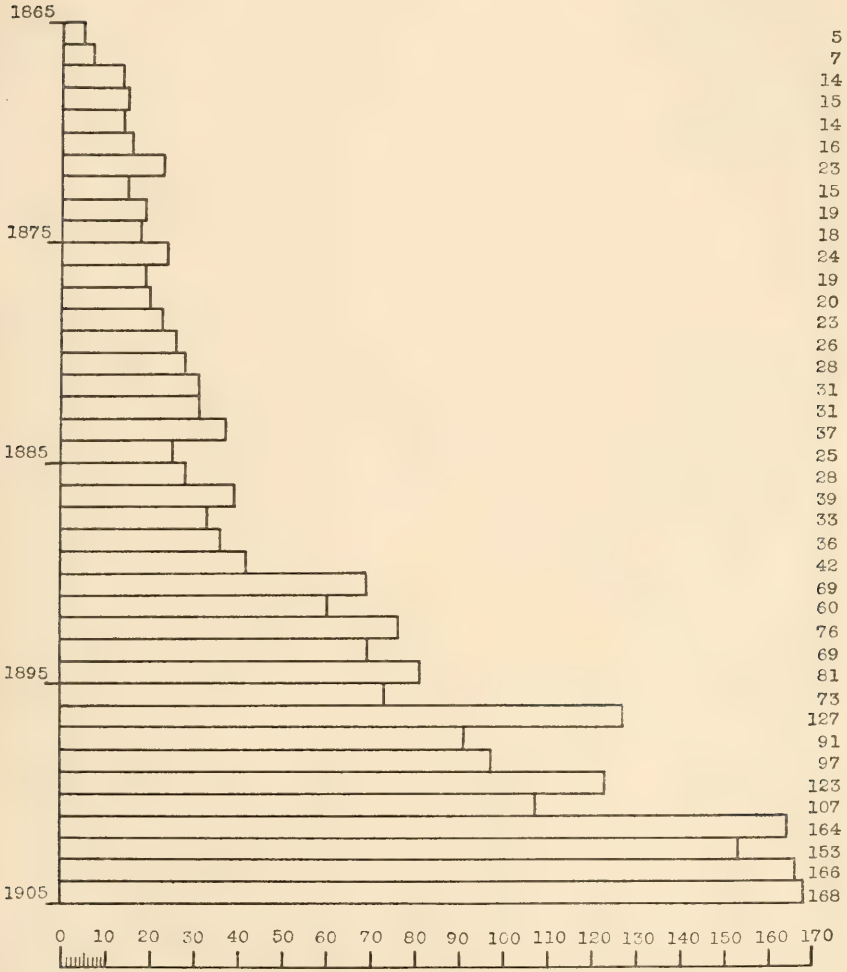


FIG. 1.—Diagram of the annual number of deaths registered in England and Wales as due to anæsthetics in the years 1865—1905.

Now, this is a heavy price to pay for even the great boon of anæsthesia; for it is an unnecessary price—a toll levied in

all good faith by reason of a neglect of the most elementary knowledge of the physical and physiological properties of chloroform.[1]

I do not say that such neglect is universal, and that there are not exceptional administrators of experience and natural skill such as to entitle them to be considered "safe," but I do say that the general practice of the overwhelming majority of persons, whether medical or non-medical, who are necessarily called upon to administer chloroform, is dangerous, and must unavoidably kill a certain number of patients and endanger the lives of many more, and produce an incalculable amount of alarm and uncertainty in connection with anæsthesia.

And I shall hope to show in the course of this article, so as to be understood by any educated person, medical or non-medical, that this heavy price is paid for lack of a little

[1] I do not think it necessary to enter here into any detailed discussion of the value of these statistics. It has been urged in mitigation of the figures that (1) they include many cases in which death has occurred not *by*, but only *after*, chloroform; and that (2) we should take into account the greatly increased number of operations performed under anæsthesia.

I think that the first error is far outweighed by the opposite error of attributing to other causes deaths that have in reality been due to the anæsthetic. A large proportion of cases of deaths undoubtedly due to chloroform are never published, or are attributed to other causes. How many it is impossible to say. Some years ago, when I went closely into the matter, I found in the case of one hospital, at which two cases had been reported in the year, that nine cases had actually occurred. The late Prof. Julliard, of Geneva, found that twenty cases of death by chloroform had occurred at Geneva, of which three only were reported. And only last January a London coroner, in opening an inquest, stated that "this is the thirty-ninth case of the kind from —— Hospital in the course of six and a half years."

In *The British Medical Journal* of January 25 (p. 202), a case of death during anæsthesia is reported by an anæsthetist under the title "A Fatal Case of Status Lymphaticus"; and the previous pages of the same issue contain an elaborate argument by another anæsthetist to the effect that death during chloroform anæsthesia is so frequently associated with "status lymphaticus" that it may be asked whether death under chloroform ever occurs apart from that condition.

Clearly the price of anæsthesia, as indicated in the returns of the Registrar-General, must be below rather than above the mark. With regard to the probable increased number of operations under anæsthetics during the last half-century, no doubt it has had some influence on the increased number of deaths noted for the later than for the earlier years, but it can hardly account for the figures of the last two decades, in which, while the reported deaths have more than doubled—533 and 1,269—the number of operations can hardly have increased in the same proportion.

elementary science—not science expressed in Græco-Latin neologisms, but science of the A B C character, consisting of simple arithmetical measurements, far less complex and learned-sounding than much of the science that is dispensed by board-school teachers and extension lecturers, but for lack of which even a doctor of medicine is not qualified to administer chloroform.

Let me premise in the first place that it is totally futile in the case of any poison, whether it be called strychnine or alcohol or aconite or morphia or chloroform, to discuss sources of danger, antidotes, diathesis, idiosyncrasy, etc., etc., without knowing how much strychnine or alcohol or chloroform has been put into the body. It is comparatively easy to learn how much strychnine will kill, rather less easy to know how much alcohol will intoxicate, comparatively difficult to determine how much chloroform will anæsthetise.

Alcohol is more or less measured out, by glass or bottle, and we know that the subject gets more or less drunk after more or less drink; knowing this we are justified in observing that subjects differ, and that qualities of liquor vary; and if necessary we can go on to consider effects of adulterations and effects of idiosyncrasy. But obviously we could do nothing of the sort unless we could measure quantities of poison swallowed.

But in the case of chloroform, which is administered by inhalation through the lungs, the effects of adulteration and the effects of idiosyncrasy have been discussed in the absence of any approach to such a measurement. The patient has as a rule inhaled an unknown quantity of chloroform. As a rule the administrator has not the slightest idea what the quantity has been, and a fatal accident that has in all probability been caused by overdose is put down to idiosyncrasy of patient or impurity of chloroform.

Is it not clear that the first necessary step to take, previous to any possible rational discussion of idiosyncrasies and impurities, is to find means of measuring the quantity of chloroform absorbed, or at any rate of measuring the quantity of chloroform in the air inspired?

My attention was forcibly directed to this question in 1890, in connection with physiological experiments. Whereas in my previous clinical experience I had had occasion to administer

chloroform fairly often in the rough-and-ready fashion of the Edinburgh school, without mishap or alarm, in my subsequent laboratory experience I frequently lost animals by overdose of chloroform, and for a time I took to ether instead.

From this I was led to make a long series of experiments on isolated nerve with ether and with chloroform vapours at all kinds of percentages in air. Using the excitability of nerve as my touchstone, I found that 10 per cent. chloroform vapour was immediately and irremediably fatal, while ether vapour at much higher percentage caused complete but only temporary inexcitability. I studied in the same way many other anæsthetic drugs—the chloromethanes and chloroethanes especially, and chloroform itself at percentages from 0·5 to 5 per cent. I came to the conclusion that chloroform is physiologically seven times as powerful as ether, that as a certain and controllable anæsthetic, chloroform is the best of the chloromethanes, and preferable to any of the various chloroethanes that have been recommended from time to time for clinical use, but that the safe administration of chloroform requires the continuous and uniform inhalation of chloroform and air at between 1 and 2 per cent.—or, as I then expressed it for the sake of emphasis, "not below 1 per cent., not above 2 per cent."

In the discussion that took place on the communication of these results at the meeting of the British Medical Association at Montreal[1] (1897) and in the following year at the Society of Anæsthetists, the principal points of opinion elicited were to the effect that it was certainly desirable that chloroform should

[1] Waller: "The Action of Anæsthetics on Nerve; Ether and Chloroform," *Brit. Med. Journ.*, November 20, 1897.

Waller: "On the Dosage of Chloroform," *Brit. Med. Journ.*, April 23, 1898.

Waller: "On the Administration of Chloroform to Man and to the Higher Animals," *Lancet*, November 28, 1903.

Waller: "On the Physical Relation of Chloroform to Blood," *Proceedings of the Royal Society*, Vol. 74, 1904, p. 55.

Waller and Geets: "The Rapid Estimation of Chloroform Vapour," *Brit. Med. Journ.*, June 20, 1903.

Waller: "Chloroform Estimation by Densimetry": "Ether Estimation by Densimetry," *Proceedings Physiological Society*, July 11, 1903.

Waller and Collingwood: "Estimation of Inspired and Expired Chloroform," *Proceedings Physiological Society*, February 25, 1905.

Waller: "A Physiological Contribution to the Problem of Chloroform Anæsthesia," *Brit. Med. Journ.*, December 24, 1904.

Waller: "On the Action of Anæsthetics," Presidential address to the Physiological Section of the British Association, Leicester, 1907.

be administered with plenty of air, but that it was practically very difficult if not impossible to secure the administration of the vapour between any definite limits of percentage.

This opinion was, I think, in the main correct. Snow's inhaler, in which the patient inspired through a bottle containing liquid chloroform, had been found to be not free from danger, the *estimated* percentage was rather high (4 per cent. or 5 per cent.) and the apparatus fell into disuse until recently, when it was revived under a slightly different form by Vernon-Harcourt, and favourably reported on by a committee of the British Medical Association.[1] The percentage of delivery of this modified form is adjusted to be from 0·5 to 2 per cent., but in my opinion the percentage scale with which the instrument is furnished is no real indication of the actual percentage of delivery. The method is the everyday method of the laboratory, where prompt rather than safe anæsthesia is required; but obtained at a price of accidental deaths by overdoses with which every physiologist is familiar.

Paul Bert's method to deliver to the patient chloroform and air at known percentage from a large gasometer proved to be quite impracticable.

Another French apparatus, that of Raphael Dubois, has fallen out of use in France, and has been condemned in this country as being cumbrous and expensive. It is, as I have elsewhere stated,[2] a very safe apparatus indeed, and my opinion has been confirmed during the last three years by the far more extensive experience of Dr. Paul Chapman, of Hereford. I believe, however, that the method is inferior both in certainty and in convenience to that which I shall finally describe.

An apparatus of my own,[3] called the wick-vaporiser, based on the principle of the carburettor of a motor-car, and adjusted to deliver by the evaporation of chloroform from 1, 2, or 3 wicks, 1, 2, or 3 per cent. of chloroform vapour, has rendered good service in the laboratory, has proved satisfactory in a limited number of trials in hospital, but is open to an objection that applies in more or less degree to all other forms of apparatus

[1] *Brit. Med. Journ.*, July 1903.

[2] "An Examination of Apparatus proposed for the Quantitative Administration of Chloroform," *Lancet*, July 9, 1904.

[3] "The Wick-Vaporiser," *Proceedings of the Physiological Society*, August 19, 1904; *Journal of Physiology*, vol. xxxi.

I have examined: viz. the graduation, however carefully made in the laboratory, is illusory when copied by the instrument-maker, and still more illusory in the hands of an anæsthetist.

The Roth-Dräger apparatus is designed to supply a mixture consisting of a measured volume of oxygen and a measured volume of chloroform vapour from a measured number of drops of liquid chloroform. The apparatus has been used largely in Germany during the last four or five years. I tested it in 1904, and found that the delivery is approximately in accordance with the graduation of the scale. The apparatus is, however, cumbersome and complicated, more so than the Dubois.

But I do not propose to encumber these pages with the detailed description of particular apparatus. All I wish to do is to make good the point that the necessity of measurement has given rise to measuring apparatus in France, in England, and in Germany. All such apparatus applies one or other of two principles—the chloroform mixture being supplied to the patient on the vacuum system—Snow, Vernon-Harcourt; or on the plenum system—Dubois, Junker, Waller, Roth-Dräger. On the vacuum system, the patient inspires air through a vessel containing liquid chloroform by a broad inlet tube and a closely fitting face-piece. On the plenum system the patient inspires from a freely open face-piece in which an excess of chloroform and air of required percentage is maintained by a pump. Obviously the former method is more difficult to apply perfectly than the latter.

The most serious objection to every sort of graduated apparatus is, however, the fact that the graduation, valid in the laboratory to an error of perhaps 10 per cent., is liable to variations of 100 or 200 per cent. in hospital use. The value of any scale of any sort of graduated apparatus used under clinical conditions is less than none, for the graduation is misleading. Variations of temperature, of ventilation, agitation, etc., may at once cause the unit percentage to rise to 2 or 3, or to fall to $\frac{1}{2}$ or less, and the scale becomes completely misleading—1 may mean 2 or 0·5; 2 may mean 4 or 1; 0·5 may mean 1 or 0·25—and any discussion as to what percentages are safe or dangerous is waste of time. Indeed, when one asks by what methods percentages are determined, he must marvel at the facility with which it has become customary for anæsthetists to talk about this or that percentage

of chloroform. All the same, this loose talk in terms of percentage is a considerable step in advance of the state of matters a few years ago, when anæsthetists were accustomed to scout the possibility of any sort of measurement, and to judge of the action of chloroform solely by its result upon the patient. Obviously, under such conditions, the only safe anæsthetist was the experienced anæsthetist, the man who had learned to recognise danger as soon as danger became visible. No man can be thus experienced from the outset, some men become thus experienced more rapidly than others, others never become thus experienced. Is it not, therefore, self-evident that in every few thousand administrations there must be cases of serious danger or death, and that in every single administration there must be anxiety or alarm? And may it not be expected of science, which is measurement, that the heavy price of anæsthesia should be reduced? I assert again what I have already asserted repeatedly in medical circles—at Montreal before the British Medical Association, at the Society of Anæsthetists in London in 1898, at Johannesburg to the Physiological Section of the British Association in 1905, in many communications to the *British Medical Journal* and *Lancet*—that the price need not be paid, or, at least, may be greatly reduced, by the application to medical practice of two or three simple lessons of arithmetic learned in the physiological laboratory.

It was estimated by Snow[1] that 18 minims of chloroform in the blood of a patient will produce anæsthesia, and that double the amount is fatal.

Gréhant estimated that the blood of animals killed by chloroform inhalation contained about 50 milligrammes per 100 grammes.[2] This proportion would be about 2½ grammes in the blood of an average person.

Buckmaster and Gardner[3], by a more precise method, arrived at an almost identical result. The amount of chloroform in the blood of an animal killed by inhalation of strong vapour was from 40 to 60 milligrammes per 100 grammes; that in the blood

[1] Snow, *On Chloroform and other Anæsthetics*, 1858. 18 minims is approximately 1 c.c. of liquid chloroform, or 300 c.c. of chloroform vapour. 1 gramme of liquid chloroform gives approximately 200 c.c. of vapour.

[2] Gréhant et Quinquaud, "Dosage du Chloroforme dans le Sang d'un Animal anesthésié," *Comptes Rendus de l'Académie des Sciences*, xcvii. 1883, p. 753.

[3] Buckmaster and Gardner, "The Estimation of Chloroform in the Blood of Anæsthetised Animals," *Proceedings of the Royal Society*, vol. 79, 1907, p. 309.

of an animal completely anæsthetised was 20 to 40 milligrammes. And following out the percentage in the course of anæsthesia, they called attention to the fact that at the very outset the percentage commonly reaches a maximum value within the first minute or two, and thus gives rise to "a first danger point" during the induction of anæsthesia.

As ordinarily administered, it is quite possible that a patient should take into the lungs in one minute 10 litres of air, containing 4 per cent. of chloroform vapour, *i.e.* 400 c.c., of which one-half may be at once absorbed by the pulmonary blood and carried to the heart, *i.e.* 200 c.c. or 1 gramme, or one-half the quantity reputed to be lethal. Merely by a single deep gasp after the breath has been held, it would be quite possible for a patient to take suddenly into his lungs perhaps 100 c.c. of vapour, or half a gramme of liquid chloroform. Is it to be wondered at that a heavy price is paid for the boon of anæsthesia? Is it not, rather, matter for surprise that the price is not heavier than it is?

The principal condition upon which the required state of anæsthesia depends is the mass of chloroform present in the inspired air, or, in other words, on the tension of chloroform vapour in the lungs. And it is important that, as far as possible, the percentage (or tension) of chloroform vapour in the inspired air should be kept as constant as possible by the continuous administration of chloroform at low percentage. The intermittent and irregular administration at high percentage should, as far as possible, be avoided. In comparison with the fulfilment of this principal condition all other considerations are of subordinate importance—the fact that the administration should be commenced at relatively low percentage, and once anæsthesia is induced that it can be maintained at low percentage; the fact that patients differ in their susceptibility to anæsthetics; the fact that more or less profound anæsthesia is required, according to circumstances; and many other detailed facts, to the scientific control of which it is primary that we should know how much chloroform is actually delivered to the inspiration of the patient, or, rather, what is the actual percentage and tension of chloroform vapour in the inspired air.

Some ten years ago I said that the percentage should be between 1 and 2. During the last few years I have elaborated a ready method of estimating that percentage, and have

attempted to devise a ready method of delivering chloroform vapour and air between the required limits.

I have at last hit upon a combined method of estimation and of delivery that has proved itself to be an admirable laboratory method, and that will, I believe, prove to be of great service as a hospital method of exact administration.

The arithmetical data upon which the method depends are as follows:

A litre of chloroform vapour weighs .	5·3	grammes
„ air „ „ .	1·3	„
Difference	4·0	„
Or difference per 1 c.c. .	4·0	milligrammes

A litre of chloroform and air at 1 per cent., or 990 c.c. of air + 10 c.c. $CHCl_3$, weighs 1·34 grammes, and every 40 milligrammes of weight in a litre flask or bulb of mixture indicates 1 per cent. of chloroform vapour in the mixture—or in a 250 c.c. bulb each centigramme indicates 1 per cent. This affords a ready means of estimating from time to time the percentage of chloroform vapour in mixtures of chloroform and air, and I have used it extensively as a means of calibration and control of apparatus. But, obviously, it is not a method for use outside the laboratory.

But the next step, by which I sought to obtain for the laboratory a means of estimating from moment to moment, and recording, the fluctuations of percentage taking place in the chloroform mixture delivered to an animal, and of varying the percentage as desired for the experiment, put me in possession of an instrument which at once fulfilled its laboratory purpose and at the same time is obviously capable of being transferred to the operating theatre.

Instead of weighing in air a bulb full of chloroform mixture, I weighed, or rather counterpoised, a bulb full of air in a jar traversed by the chloroform mixture; the bulb, of course, rose and fell as the mixture was made more or less dense by more or less chloroform vapour. The pointer of the balance was then graduated in chloroform percentages by appropriate weights—increments of 40, 80, 120 milligrammes for 1, 2, and 3 per cent. $CHCl_3$ with a litre bulb.[1] A light pen fixed to the beam of the

[1] I have not talked about temperature and pressure corrections, which should be taken into account when required, and ignored when not required. For

balance and a smoked cylinder served to give a record of the rise and fall of the bulb with rise and fall of chloroform percentage, and incidentally served the useful purpose of damping the oscillations of the beam and pointer. In order to avoid accidental fluctuations of the percentage delivered to the animal, it was advisable to use a vessel of considerable volume containing the mixture on its way to the animal. I used the case of the balance for this purpose. Air was pumped into it through or over the surface of chloroform by the ordinary respiration pump or by a bellows, and went on by a second tube to the tracheal cannula or mask. The large capacity of the balance case—in this case 30 litres—proved to be suitable for the induction of anæsthesia and for its safe gradual modification. The chloroform percentage rose from zero to 2 per cent. in about two minutes; the lag of voluntary diminution and increase was about ten seconds; the pointer could at will be kept perfectly steady at any desired percentage. Finally, I may remark that for all ordinary purposes of the laboratory a comparatively coarse balance is best adapted. In the apparatus now in daily use the graduation is from 1 to 3 per cent., which gives records of 6, 12, and 18 mm. amplitude.

Judging by the comments of visitors to the University of London, acquainted with the various haphazard methods in use for producing and maintaining anæsthesia of the human subject, and witnessing for the first time the ordinary procedure followed in the physiological laboratory for the producing and maintaining of anæsthesia of animals, the usual thought aroused seems to be one of regret that the human subject cannot be anæsthetised with similar uniformity and safety.

My own feeling is one of intense surprise, that the clear practical experience of the laboratory should be of so little use to the medical profession, and that year by year the death-roll of chloroform anæsthesia should continue undiminished.

Occasional attempts have indeed been made in France, in Germany and in England, to bring graduated apparatus into use, and have met with a certain amount of success in the

ordinary temperatures (18° C.) and pressure (760 mm. Hg) a bulb of 1054 c.c. would be required for these increments. Or if, as was the case of the particular balance now in my hands, the bulb had a capacity of 870 c.c., the counterpoising weights for 1, 2, 3 per cent., should be taken as 33, 66, and 99 milligrammes.

hands of a few anæsthetists. But for one reason or another, graduated apparatus has not met with general favour; instruments have been too dear, or too troublesome, or have failed to fulfil the promise of their inventors and advertisers. Each inventor, whether French or English or German, has had his instrument patented; and the consequence has been that each instrument has been advertised as perfect, whereas as a matter of fact no instrument can be perfect—every instrument requires to be used intelligently.

I think it may be useful to describe the ordinary daily practice of this laboratory towards animals, and to indicate as briefly as possible how I should propose that a similar procedure should be applied to hospital anæsthesia. And I shall at once premise, in reply to the inevitable objection that the method is too troublesome for hospital use, (1) that it is not too troublesome for daily use in the laboratory for animals, (2) that several thousand animals have been anæsthetised in this laboratory during the last five years, without the accidental loss of a single animal, and (3) that, even admitting that the procedure is more troublesome than the ordinary practice, it is not unreasonable to expect as much trouble to be bestowed upon the safe anæsthesia of a patient in a hospital as is bestowed upon an animal in a laboratory. In point of fact, the trouble of application would be smaller in the case of man than it is in that of an animal.

The procedure in this laboratory as regards animals is as follows:

First step.—The animal is placed in a closed glass chamber (a large bell-jar, or a small cupboard with plate-glass front), into which chloroform-and-air of desired percentage is pumped. The latter is provided by pumping air by a small electric motor through an ordinary wide-mouthed bottle containing liquid chloroform, into a large-mixing chamber (capacity = about 30 litres), containing the chloroform balance and provided with an inlet from the chloroform bottle and an outlet to the animal chamber. The flow of air is rendered uniform and of suitable volume per minute by means of an elastic reservoir and a perforated stop on the course of the supply tube. The percentage of the mixture administered is watched on the pointer scale (and if desired recorded by a light pen). It is regulated by varying the depth of a tube in the chloroform bottle and by

admitting more air to the mixing chamber. In general, anæsthesia is induced by chloroform and air at 2 per cent., and the animal is kept under anæsthesia at 1 per cent. until required.

Second step.—The anæsthetised animal is removed from the bell-jar or cupboard, for the operation of tracheotomy. The outlet tube of the mixing chamber is attached to the tracheal tube, and anæsthesia is maintained by a mixture at between

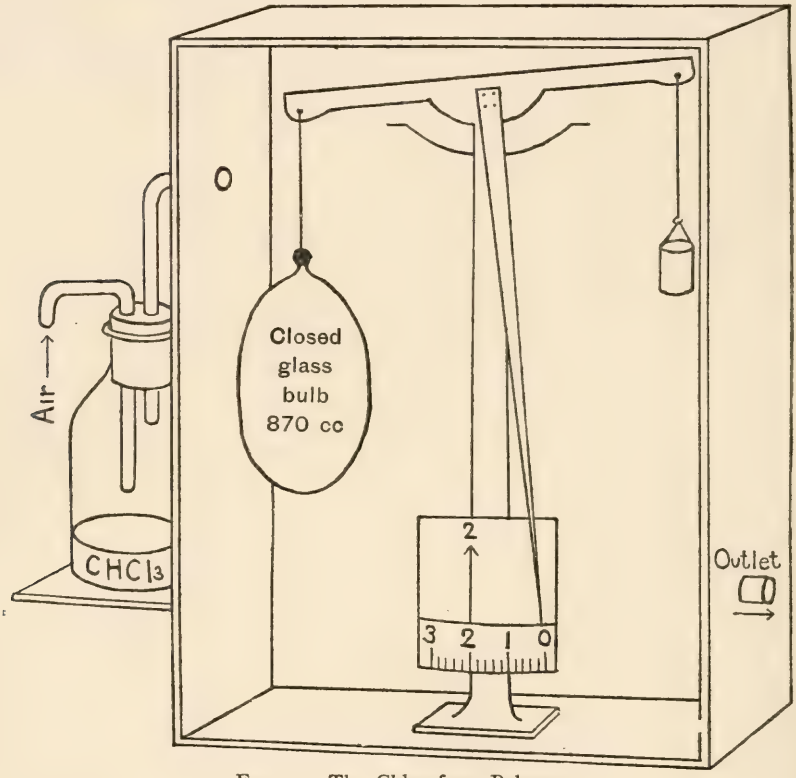


FIG. 2.—The Chloroform Balance.

1 and 2 per cent., as shown by the index of the chloroform balance. The chloroform-and-air is taken by the animal by its ordinary respiration, or supplied to the animal by the action of the pump (in which case the elastic bag and perforated stop are removed from the supply tube). In either case the anæsthetic vapour is under slight positive pressure—*i.e.* it is delivered on the plenum system.

The *procedure in hospital* is (or would be) simplified by the fact that the first step necessary in the case of animals, viz. anæsthesia in a confined space, is not necessary for the human subject. Obviously, also, tracheotomy is omitted; all that is required for the human subject is an open mask or face-piece at the end of the delivery tube. For since the delivery of chloroform to the patient is on the plenum principle, and such pressure as exists in the mixing chamber and delivery tube is positive, length of tube is immaterial, and does not place any extra work upon inspiration by the patient. All the apparatus required by the anæsthetist at the operating-table consists of the tube itself, and the face-piece or other terminal contrivance; the pump, the chloroform bottle, the mixing chamber, and the chloroform balance are at a distance from the operating-table, out of the way, but not out of sight. The size of the mixing chamber (30 litres) ensures the continuous and uniform supply to the patient of chloroform (or ether) vapour at known and visible dilution. The indication of percentage is easily verified, and is visible to all persons present. The concentration, which, by reason of cooling of the chloroform, automatically remains below 3 per cent., can be varied at will with sufficient rapidity, as shown by the indicator, and it cannot be suddenly augmented to a dangerous amount. The attention of the anæsthetist is free to be wholly bestowed upon the state of the patient, in accordance with which the strength of vapour is raised or lowered, and *seen* to be raised or lowered. (At the cost of a very trifling additional trouble, a permanent record can be taken of the strength of vapour employed during the whole time of its administration.)

The apparatus in its laboratory form is not very portable. And although, no doubt, it may be practicable to render it more portable, I prefer at present to keep to the dimensions with which I am familiar, and to advise its use chiefly as a hospital fixture, set up in the operating theatre and in the room or rooms in which patients are prepared for operation. I am convinced that an installation of apparatus of this character would go far to remove the possibility of prolonged series of fatalities such as that mentioned in the footnote to p. 612, and to allay an incalculable amount of anxiety in the minds of all those who know. And as regards the general public, who at present do not know, I am convinced that if the serious

misfortune of an unreasoning dread of anæsthetics is to be avoided, the danger of anæsthesia must be reduced to whatever may be its unavoidable minimum, by applying in the hospital the clear teaching of the laboratory.

A direct indicator of the percentage of chloroform in the air delivered to the inspiration of a patient is, in my opinion, a valuable safeguard. It is not difficult to secure; it is legible at a glance. I do not say that its use would abolish all danger, but I do assert that the common knowledge of the physiological arithmetic of chloroform would go far to diminish the excessive price of anæsthesia.

RECENT RESEARCHES ON CHLOROFORM ANÆSTHESIA

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Any one who at the present time reflects upon the advances which have taken place in medical practice within the last twenty-five years will easily recognise that the introduction of antiseptic and aseptic methods—for which all mankind is under a lasting debt to Lord Lister—has largely increased the frequency of surgical operations. The frequency with which general anæsthetics are employed has consequently also augmented to an equal or even greater extent, and it may be admitted that the safe administration of such a drug as chloroform is to a large extent dependent upon the skill of the individual anæsthetist. However, deaths may, and do, occur during anæsthesia. Life may be lost before an operation has been commenced, and the cause or causes of such an accident has been the subject of much useless speculation, and also of some valuable experimental work on the physiology of anæsthesia. The whole science and art of medicine advances sometimes at a slow, sometimes at a quicker rate, but any given degree of progress is almost entirely regulated by those additions to knowledge which are founded upon exact experiments carried out in laboratories.

During the past few years the subject of anæsthesia by

chloroform has been under the consideration of a special committee appointed by the British Medical Association.[1] The experimental work thus initiated has proved of much service, especially in indicating the limit-value of the chloroform vapour which can be safely inhaled. The introduction of an inhaler by Vernon Harcourt for the administration of chloroform with safety is also the direct outcome of this work. The simplest and quickest way to determine the percentage of chloroform vapour in air is by a method suggested by Waller,[2] which depends upon the proportional increase in weight which known volumes of air and chloroform exhibit, compared with the same volume of air. The purpose of this paper, however, is to draw attention to recent work on chloroform anæsthesia which has been carried out in this country and in France. The activity of observers in Germany has not been directed to this particular inquiry.

Besides chloroform, some hundreds of substances have been shown to possess in different degrees well-marked anæsthetic and narcotic properties. All forms of life, the simplest and the most complicated, unicellular and multicellular organisms, can be shown to exhibit very similar phenomena in response to minute, moderate, and toxic doses of those drugs which are grouped as anæsthetics; and it is probable some single fundamental type of interaction which takes place between the anæsthetic and the protoplasm or bioplasm of cells, will be found to take place, and that upon this fact a rational explanation of the anæsthetic process will be given. The condition finally established by increasing any given anæsthetic is one of profound intoxication, and a state of narcosis is induced in the higher animals, owing to the successive interference with the excitability of the cortex of the brain, of the grey matter of the spinal cord, and of the grey matter of the spinal bulb or medulla oblongata. These parts of the central nervous system become inactive, and a progressive paralysis of the nerve cells becomes established, in which the sensory and receptive apparatus is probably impaired before the motor. It is beyond dispute, as any one must admit who is familiar with the subject, that the anæsthetic state is a condition where

[1] *British Med. Journal*, July 12, 1902, July 18, 1903, July 23, 1904, July 22, 1905, July 14, 1906.

[2] Waller, *Proc. Physiological Soc.* 1903.

the tissue elements, or cells of the body, are poisoned in different degrees, and the cells of the central nervous system in higher animals exhibit a peculiar elective or selective power in picking up such a drug as chloroform, compared with other portions of the excitable tissues or neuro-muscular apparatus of the body. No matter by what particular hypothesis this selective power is explained, it is equally certain that chloroform does not actually accumulate in the tissues, or remain permanently held by protoplasm, for a restitution of the normal functions of the whole body is always to be seen, provided that the interference with function has not been of too long a duration.

As an explanation of the anæsthetic state some observers on insufficient grounds have attributed this to a local anæmia of the cerebral cortex. But it is known that this view is not in accord with experimental evidence, for the opposite occurs in the early stages of chloroform narcosis; and as Roy and Sherrington and also Hürthle have demonstrated, the blood-flow through the brain is actually increased. In profound anæsthesia, the bulbar centres—those complex nerve-cell aggregations which physiologists speak of as the vaso-motor centres, which control the bore of the smallest arteries, so that these are in no sense inert tubes of constant diameter, the respiratory centres controlling the muscular movements of the thorax, and the cardiac nerve-centres, which govern the liberation of energy by the heart muscle—become paralysed. Frequently these centres are finally poisoned in the order in which they have just been mentioned, and then, owing to a vaso-motor paralysis, which is particularly a feature of chloroform poisoning, such a quantity of blood may accumulate in the dilated blood-vessels that a true cerebral anæmia may occur. Here it may be mentioned that experiments upon animals have yielded incontestable evidence that among mammals the vaso-motor nervous mechanism is more perfectly developed in a physiological sense in man than in the apes, in the apes than in the carnivora, in these more than in rodents. As Leonard Hill[1] has shown, the explanation of this perfected mechanism in man is related to his erect posture, and the circulation of blood through the brain is maintained at a normal value, whether an animal is placed in a horizontal position or in the feet-down or head-down position.

[1] *Journal of Physiology*, vol. xviii. 1895.

From two volumes published last year by a well-known anæsthetist[1] on the chloroform problem, a few remarks may be abstracted, in order to show how the phenomena witnessed in chloroform anæsthesia may lead a skilled clinical observer to views for which at present there is no sufficient experimental evidence, though it is impossible for any one to deny that the deprivation of oxygen may play a very important part in throwing the cells of the neuro-muscular apparatus out of action. The author considers that "chloroform and ether are typical examples of a group of agents which possess the power of abstracting oxygen (from the blood) without otherwise injuring the blood."[2] Again, "all narcotic agents are oxidisable, and cause all their results (direct and indirect) by abstracting oxygen from the blood."[3] "They do not act directly upon the cerebral centres, but indirectly through the intermediation of the -oxy factor, which it would appear is the only known cause of the suspension of their functions."[4] Further, he states that "it is impossible for chloroform to remain in the blood without becoming oxidised; but if there be an excess in the circulation, *i.e.* such an amount as will require more for its oxidation than can be supplied by blood, what influence does the rest exert?"[5] The purpose of this article is not to criticise the views held by any one; but the ideas put forward in this way, supported as they are by no sufficient evidence, are in absolute contradiction to a knowledge which has been most slowly built up by experimental methods. All the evidence acquired by experiments to determine this particular fact, whether any oxidation processes whatever are possible within the blood-stream, has uniformly shown that no measurable consumption of oxygen under any circumstances, even by a substance so easily oxidisable as pyrogallic acid, can be detected with certainty while the blood is within the vessels. It is a cardinal fact, and one accepted by every physiologist, that the consumption occurs within the tissue cells of the body, and that this is dependent entirely, not upon the supply of oxygen, but upon the requirements of the entire organism. The evidence for this is to be found in any physiological text-book. For example, Schmiedeberg found that such easily oxidisable

[1] *The $CHCl_3$-problem*, by Richard Gill. 2 vols. 1906.
[2] Vol. ii. p. 275.
[3] Vol. ii. p. 278.
[4] Vol. ii. p. 279.
[5] Vol. ii. p. 267.

substances as benzyl alcohol or salicylic aldehyde undergo no change within the blood-stream; but that the substances are easily oxidised to benzoic acid and salicylic acid when the blood-flow passes among the cells of the kidney.

The explanation which is advanced—that anæsthesia is due to the abstraction of oxygen by chloroform—rests on no certain basis, for it is quite easy to anæsthetise a frog when all its blood is replaced by ·65 per cent. sodium chloride. Moreover, all animals, including man, who live at varying altitudes from the sea-level to 10,000 ft., are luxuriously supplied with oxygen, so that the amount available far exceeds the need. As will be shown subsequently, the actual amount of chloroform in the blood during anæsthesia is known, and assuming, which is not the case, that it is easily oxidised, the amount of oxygen which might be abstracted in this way would not produce any symptoms at all, except in so far as the oxidation products could exert an effect, and still less possible would it be for a state of anæsthesia to be established by so small a diminution in the oxygen-content of the blood. The destiny of the chloroform in the blood is to be exhaled; and if any amount of it is oxidised this takes place, not in the blood, but in the tissues of the body. Kast [1] and Zeller,[2] also W. H. Thompson,[3] have found an excess of chlorides in the urine after chloroform narcosis; while some observers—Wagener,[4] Thiem and Fischer[5]—state that chloroform as such can be recognised in the urine. An excess of chlorides is not conclusive evidence that the drug is oxidised, for these are increased, but not to the same extent, after anæsthesia by ether.

Experimental evidence that chloroform may be decomposed within the organism has been furnished by Desgrez and Nicloux,[6] who found small quantities of a combustible gas which might be hydrogen methane or carbonic oxide in normal blood. 1000 cc. of this yielded 1·2 cc. of a gas which was apparently carbonic oxide. In the same quantity of blood from animals deeply chloroformed larger amounts were found—in one case 6·9 cc. of carbonic oxide. This increased amount was

[1] *Zeitschr. f. physiolog. Chemie*, xi. 1887, and *Jahresber. f. Tierchemie*, xviii. 1888.
[2] *Zeitschrift f. physiolog. Chemie*, viii. 1883.
[3] *Proc. of Physiological Soc.*, January 21, 1905.
[4] *Jahresbericht f. Tierchemie*, xxx. 1900.
[5] *Chem. Zentralblatt*, i. 1890.
[6] *Arch. de Physiologie*, No. 2, 1898.

believed to arise from a decomposition of chloroform. These observations have neither been confirmed nor refuted, but in any case the amount of the drug which was decomposed would be small.

The most varied types of living animal and vegetable cells respond in an identical manner to the action of chloroform, a drug which is seven to eight times as toxic as ether (Waller). Exceedingly minute doses stimulate living protoplasm; thus, the time of inflorescence of the lilac or azalea is quickened by chloroform vapour.[1] With progressively increasing amounts of the drug, the energy discharges of any organism decrease, and finally disappear with a lethal amount. Both individual cells and organisms differ in the degree of their reaction to anæsthetics; but with a sufficient concentration of the drug, the final result is death. Experiments have shown that dogs and other animals are effectually killed by amounts of chloroform which are incapable of producing anæsthesia—in other words, the metabolic or nutritional processes of the body are profoundly affected, the temperature falls, and death occurs. This phenomenon was clearly described by Paul Bert[2] in 1883, and has been more recently studied by B. J. Collingwood.[3] The following table is constructed from experiments carried out on dogs by Paul Bert:

Percentage of chloroform vapour in air.	Results.	Hours from commencement of administration till death.
·8	No anæsthesia	9–10
1·2	Diminished sensibility	6–7
1·6	Anæsthesia slowly induced	4
2·	Anæsthesia in a few minutes	2–3
2·4	„ „ „	1·7
3·	„ „ „	·66
4·	„ „ „	·5
6·	„ „ „	·005

It will be seen that the toxic action of chloroform profoundly checks the nutritional or metabolic phenomena of the body; when a low percentage is inhaled an enormous quantity of chloroform can pass into and out of the body without producing

[1] E. Lemoine, *Jour. of Royal Hort. Soc.* October 1903, and Leblanc, *Soc. Cent. d'Hort. de Nancy*, 1906.

[2] *Comptes rendus de l'Acad. d. Sc.*, t. xcvi. p. 1831, 1883.

[3] SCIENCE PROGRESS, vol. i. p. 12.

any obvious effect except a fall in temperature. In this its action closely resembles alcohol, which has been shown by Tarchanoff to impede growth and check the development of the excitable sensori-motor regions of the cortex of the brain. Chloroform also appears to exert a marked influence on the growth of animals. Experiments have been carried out for a period of five months on kittens from the same litter and of equal vigour, which show that there is a retardation of growth, estimated by weighing, in young animals which were anæsthetised up to the point at which the corneal reflex just disappeared, twice a day. Animals, however, like plants, exhibit increased metabolic activity subsequent to this treatment, and their rate of growth more than compensates for the retardation.[1]

The Relations which may exist between Chloroform and Blood

It has already been stated that the condition of anæsthesia can be induced in isolated cells or in organisms which possess neither a blood system nor a nervous system. The condition can be established in any living thing, no matter how low or how high may be its organisation. How the anæsthetic state is actually produced is at present unknown, though the theory advocated by Hans Meyer[2] and Overton[3] is generally accepted as affording some sort of explanation. These observers, independently and almost simultaneously, ascribed the action of such an anæsthetic as chloroform to the fact that certain cell-constituents, such as lecithin or cholesterin, were capable of physically taking up or absorbing the anæsthetic. When this has occurred the activities of the cell are interfered with, especially in the sense that its response to excitation is diminished. The greater sensitiveness of the central nervous system, compared with other organs of the body, such as the muscles, is considered to be explained by this hypothesis, since the former is peculiarly rich in bodies, or lipoids, which are soluble in chloroform, or the same idea may be expressed by regarding lipoids as cell-constituents which pick up anæsthetics which are soluble in these. The basis for the theory

[1] Shapiro, *Proc. Physiolog. Soc.* December 10, 1905.
[2] *Archiv f. exp. Pathol. u. Pharmakol.* xlii. 1899, and xlvi. 1901.
[3] *Studien über Narkose*, Jena, 1901.

which has just been indicated rests largely upon physical experiments as to the relative solubility of anæsthetic substances in water and in olive oil. It is true that many anæsthetics, chloroform among them, are soluble in all proportions in oil, while water takes up only ·72 per cent.; but a convincing explanation of what occurs in anæsthesia is not likely to be gained by studies of this nature, no matter how accurately they are carried out; and, moreover, they will not afford an explanation of the action of such narcotics as morphia or conia. For these Overton, to whom we owe the introduction of the term "lipoid," suggests the existence of combinations between the drug and cell-protoplasm, a view which Benjamin Moore and H. E. Roaf have particularly put forward as a possible explanation for the action of all anæsthetic substances. Some of these, such as chloroform, may form easily assimilable and dissociable compounds with the living protoplasm; others, such as morphia, may form more stable compounds, and will therefore probably be more specific in their action.

The attention of Benjamin Moore and H. E. Roaf was first attracted to the subject of anæsthesia by witnessing some experiments performed by C. S. Sherrington and S. C. M. Sowton. If a mammal be killed and the heart removed, this organ can be shown to beat regularly for more than four days if it is supplied with a weak, watery solution of certain inorganic salts, provided that the liquid is saturated with oxygen gas. The heart, therefore, will exhibit a prolonged period of activity outside the body when there is no blood supplied to the organ. This demonstration we owe to F. S. Locke.[1] A concentration of chloroform, added to the liquid which feeds the heart, of 1 in 100,000, produces a constant effect; the vigour of each individual heart-beat is diminished. This effect rapidly appears, and persists for just as long as chloroform of this low but adequate concentration is bathing the interior of the heart. When the solution containing chloroform is replaced with Locke's fluid, the effect on the heart's beat disappears and the contractions regain their normal vigour, to again sink when the weak chloroform solution is substituted. From this experiment, to quote Moore and Roaf, it was clear that chloroform exerted no cumulative action on the living protoplasm of muscle; that is to say, the effect on the cardiac beat was the

[1] *Zentralbl. f. Physiol.* December 30, 1905.

reduction in vigour to a certain extent and no more. No matter how prolonged was the passage of the chloroform solution, the effect rapidly disappeared when the anæsthetic was removed. Secondly, the effect upon the living cells of the heart muscle depended solely upon the concentration (solution tension or osmotic pressure) of the chloroform in the cell for the time being; and, lastly, the effect at any moment was not at all due to the total amount of chloroform which had been supplied to the heart up to that particular time. Experiments of this nature suggested the view that the effect might be due to some unstable association or combination between the anæsthetic and the cell protoplasm of muscle, and that this existed for only so long as the pressure of the anæsthetic was maintained. Diminish this pressure to zero and complete recovery takes place, the association ceasing to exist; re-establish the pressure and the effect of the anæsthetic once more is witnessed. In the opinion of the writer no other view than this is possible. The condition of chloroform anæsthesia in man can be most satisfactorily comprehended by considering that from the commencement of the inhalation of an air-and-chloroform mixture the pressure of the anæsthetic augments in the blood, and it is this pressure which first of all forces the drug into the lymph and then into the cells of the body, some of these being more permeable and therefore more susceptible than others; the degree of anæsthetisation of the cells being due not so much to the absolute quantity of chloroform supplied, as to the maintenance of a definite pressure of the anæsthetic in the blood. From a large number of experiments which the writer has witnessed, it is clear that no definite fixed relation exists between the proportion of chloroform in the blood and the effect of the drug, for this is determined not by the absolute amount which is held, but by the actual quantity which passes into the cells of the central nervous system, so that the control of these over the liberation of energy by the organism is reduced to a minimum.

Since in the higher animals arterial blood is the vehicle by which chloroform is taken up from the surrounding medium and a certain solution pressure of the drug must be attained before anæsthesia occurs, the relations which may exist between blood and chloroform have been the subject of much investigation. The proteins of the blood, both those in the plasma and

the red corpuscles, particularly hæmoglobin, have been proved to form definite unstable compounds or physical aggregations with chloroform; and the position taken by the anæsthetic in hæmoglobin is not that of the respiratory oxygen, for the oxygen-carrying power of this protein is in no way impaired or interfered with by the presence of chloroform, though it is quite certain that during narcosis with chloroform arterial blood becomes progressively richer in reduced hæmoglobin. Evidence for the above statements was first given by Benjamin Moore and Roaf,[1] though numerous other observers, such as Pohl, Waller, Wells, and Vernon Harcourt, among others, had recognised with what tenacity chloroform is held by the blood after anæsthetisation, and how difficult it was to recover the drug; so that while the gases of the blood can be evacuated, only ·014 gramme out of ·108 gramme of chloroform in the blood can, as Waller demonstrated, be recovered.[2]

The effect of adding chloroform to blood *in vitro* was described by Preyer in 1871.[3] Formánek[4] more minutely investigated this subject, and proved that when a solution of hæmoglobin was treated with chloroform and kept at a temperature of 50°–53°C. for some time, the protein was so completely precipitated that the filtrate was free from hæmoglobin. Edie's experiments showed that precipitation occurred when the hæmoglobin solution contained from 1·5–7·5 per cent. of chloroform.[5] Even when the amount of hæmoglobin in solution varied and the percentages of chloroform added also varied, the percentage of the anæsthetic in the precipitate to the amount of hæmoglobin which was not precipitated remained constant, from which it may be inferred that the precipitate formed is of the nature of a definite chemical compound or, possibly, a definite physical aggregation.

Experiments *in vitro* have also shown that when a solution of hæmoglobin is taken, and 1 per cent. of liquid chloroform added, and the mixture shaken thoroughly, all the chloroform dissolves; no precipitate forms on standing either at the room or the body temperature. It must, of course, be remembered that experiments of this nature do not in any way imitate the conditions

[1] *Proc. Royal Soc.*, vol. lxxiii. May 1904, and vol. lxxvii. 1905.
[2] Waller, *Proc. Royal Soc.*, vol. lxxiv. June 9, 1904.
[3] *Die Blutkrystalle*, p. 104 : Jena, 1871.
[4] *Zeitschrift f. physiolog. Chemie*, vol. xxxi. 1900.
[5] Reports of Thompson Yates and Johnston Laboratories, Liverpool, vol. vi. 1905.

which occur when the vapour of chloroform is inhaled, and under no conceivable circumstances would anything like the amount of 1 per cent. of chloroform ever be found in the blood at the lethal stage of anæsthesia. In 1905 Friedrich Krüger again investigated this point.[1] He states that the precipitate described above is insoluble in water or neutral salt solutions, but is soluble in weak acids or alkalis; and from both of these the precipitate, as might have been expected, is again thrown down on neutralisation. The main interest of Krüger's work, however, lies in the fact that he has described and figured a special absorption spectrum for solutions of this precipitate; and should this observation be confirmed, it would undoubtedly greatly strengthen the views which are held by Moore and Roaf. Just as Edie has observed, so Krüger found that the chloroform-hæmoglobin precipitate was soluble in alkali; but whereas the former observer states that in solution in sodium carbonate yields the spectrum of alkaline hæmatin, Krüger describes the spectrum as one showing two bands, α and β, which occupy a position very similar to the well-known two-banded spectrum of oxy-hæmoglobin. The spectra are, however, dissimilar.

The difference between these and the effect of reducing agents can be seen from the following:

Spectrum.	Band α	Band β.	Effect of dilution with water.	Effect of reducing agents.
Hb + $CHCl_3$ Two bands α and β	Narrow	Broad intense	Disappear together or α before β	Reduced hæmoglobin and hæmochromogen
Hb + O Two bands α and β	Narrow intense	Broad	β disappears before α	Reduced hæmoglobin

Krüger considers that the effect of reducing agents justifies the conclusion that the chloroform-hæmoglobin precipitate consists of a mixture of hæmatin and hæmoglobin or methæmoglobin. Further, that the relation of chloroform to the blood-colouring matter is not that of an indifferent agent, which simply renders hæmoglobin insoluble, but that this substance is actually chemically changed, though he has not apparently considered the possibility that there might be a linkage between the drug and this protein. Formánek had already described the spectrum seen by Krüger as that of oxy-hæmoglobin, and for the present judgment may be suspended as to the exact

[1] *Hofmeister's Beiträge*, iii. p. 67, 1903.

spectroscopic characters of this body, especially as Krüger questions the accuracy of many of the existing charts of the spectra of the blood.

The facts upon which Moore and Roaf rely as proofs that a true compound or aggregation can, and actually does, take place between chloroform and cell-proteins have been elicited by several different methods which were employed for determining the maximum solubility of chloroform in water, salt solution (·75 per cent.), serum, hæmoglobin solutions, and in blood. The estimated maximum solubility at 13° C. by weight proved that chloroform has a much higher solubility in serum or hæmoglobin solutions than in saline or in water. For example, it was found that the following figures might be taken to represent the maximum solubilities:

	Per cent.
Water	·95
Saline (·75 per cent.)	·83
Serum	5·08–4
Hæmoglobin solutions or blood	6

Determinations of the vapour pressure of chloroform in water, serum, and hæmoglobin solutions were also made with a specially constructed differential densimeter.

It is well known that of the three gases which exist in blood the amounts of oxygen and carbon-dioxide taken up are not proportional to the pressure exerted by these gases; in other words, their absorption does not follow the Dalton-Henry law. The question whether chloroform is or is not taken up by blood according to this law has never been experimentally tested. A given mixture of air and chloroform possesses a definite chloroform vapour pressure in the mixture. If such a mixture is inhaled, the vapour pressure of chloroform in air at the anæsthetising value is found to be about 8–10 mm. of mercury, which was the value observed by Paul Bert. The evidence given by B. Moore and Roaf, who have measured the vapour pressures of chloroform in water, serum, and hæmoglobin solutions of equal strength to that which exists in blood, indicates that the curves of pressures and concentrations in the case of serum and hæmoglobin are such that it is clear chloroform cannot be absorbed according to the Dalton-Henry law, but that the drug is actually associated with the blood-proteins

at certain vapour pressures, a fact which is not easy to determine except at high pressures. Conversely, the absorption of chloroform by saline does, as might be expected, follow the law of absorption for varying pressures, and when the results are plotted out the curve is a straight line. At a temperature of 40° C., and at the anæsthetising value of 8–10 mm. of mercury, the coefficient of distribution between vapour-space and solvent for hæmoglobin is about 7·1, and at a room temperature of about 15° C. this would be 18.

Additional experiments performed by Moore and Roaf render the views of Overton and Hans Meyer, which have obtained such wide credence, somewhat improbable. At equal concentration of chloroform in water and saline the vapour pressure of the drug always exceeds what is found for hæmoglobin or the protoplasmic cells of the heart, brain, or muscle; in other words, the association of the anæsthetic with proteins lowers the vapour pressure, just as the tension of oxygen in the blood is low, owing to its association with hæmoglobin. The theory which ascribes the action of general anæsthetics to a relationship which becomes established between the lipoids (substances of the cell soluble in ether, such as lecithin and cholesterin) does not conform with the experimental fact that ethereal emulsions of the brain, which organ is considered to be so specifically affected by chloroform, behave exactly like water or saline solutions; in other words, obey the Dalton-Henry law as far as chloroform vapour is concerned, while emulsions of the entire brain, cells and lipoids show that this law is no longer followed, but that there is undoubted association of the anæsthetic at high vapour pressures. Further, comparative determinations of vapour pressure and concentration of chloroform vapour leave no doubt but that it is the proteid constituent, and not the lipoid material, which is responsible for the actual physical aggregation or chemical combination which takes place. Far from the anæsthetic state being due to an affinity of the lipoids of the cells for an anæsthetic, the existence of such substances in bulk, as is the case for individuals who possess a large quantity of fat, actually imprisons a quantity of the anæsthetic which is given, so that it is no longer available for poisoning the cells of the organism, which is essential if anæsthesia is to occur, for it is well known to anæsthetists that the greater

the bulk of fat in a patient the greater will be the absolute amount of chloroform required. It is known that the actual bulk of an individual is the gross weight minus the stored fat; the presence of this reserve material in anæsthetisation actually subtracts and renders useless some of the chloroform which is administered.

What may be the actual chemical and physical effect of anæsthetics on protoplasm generally is a difficult problem, and one method which may be applied to its solution depends upon a study of the differences of potential which may follow the subjection of living nerves to anæsthetic vapour of known strength. N. H. Alcock[1] has extended the work of Waller,[2] and, in particular, has investigated the effect of chloroform and ether upon the current of injury which occurs in excised living nerves. A difference of potential existing between the longitudinal and transverse section of the nerve slowly declines under normal conditions, but the difference suddenly drops temporarily or permanently according as the vapour is weak or strong (12 per cent. or more). By subjecting certain regions of a nerve to chloroform vapour, it was noticed that an increase of the injury current, roughly proportional to the strength of the anæsthetic, occurred only when the vapour reached the cross section; applied to the longitudinal surface it caused a decrease.

The resistance of nerve is not affected by chloroform, and therefore no formation of ions at the expense of the electrolytes in the nerve takes place, but the normal polarisation of the nerve is markedly diminished.

A very significant fact is noted with regard to the conductivity of nerve before and after chloroform and ether. While the polarisation of the nerve was markedly altered (as Waller had found) there was no change in the electrical conductivity proper. If this is substantiated it would show that no fresh ion formation took place, and that no splitting up of ion-proteid occurred. In a second paper,[3] Alcock showed that while there might or might not be a combination of chloroform with the proteid of the frog's skin, the electrical effects could only be accounted for by supposing the existence in the tissues of either membranes

[1] *Proc. Royal Soc.* vol. lxxi. p. 264, vol. lxxiii. p. 166, vol. lxxvii. p. 267.
[2] *Proc. Physiological Soc.* November 13, 1897.
[3] *Proc. Royal Soc.*, B., vol. lxxviii. p. 259.

or surfaces of separation, so arranged that normally certain ions could traverse the membranes and others could not, while after chloroform these membranes or surfaces were destroyed. A simple combination of proteids, as in Moore and Roaf's theory, or with lipoids, according to Meyer and Overton, with chloroform would therefore be insufficient to account for the phenomenon of anæsthesia.

The Anæsthetic and Lethal Quantities of Chloroform in the Blood.

In 1860 Lallemand, Perrin, and Duroy stated that 100 grammes of blood contained 1 cc. of chloroform vapour. This was the lethal amount. In 1883, from the results of seven experiments, Gréhant and Quinquaud concluded that 50 milligrammes of chloroform in 100 grammes of blood was the anæsthetic quantity, which was only slightly less than the amount present at the lethal stage. It will be seen subsequently how very exact were both these determinations. Pohl's work in 1890 introduced a new method for the determination of chloroform in blood, and his chief conclusions were that the quantities of chloroform in the arterial blood of dogs during anæsthesia might vary. In some cases 100 grammes of blood contained ·05 gramme, in others only ·029 or ·018 of chloroform. The average lethal amount was ·035 gramme. Pohl also recognised that the lethal and anæsthetic amounts closely approximate one to the other. For about sixteen years no further researches were undertaken in connection with this question, but it was from time to time made abundantly evident that an accurate determination of the chloroform-content of blood was one of difficulty, owing to the tenacity with which the drug was held by the blood, so that it could only in part be recovered from that liquid or from the tissues of the body. During 1906 several French observers, and Buckmaster and Gardner in this country, have renewed this inquiry, and though the methods which have been employed in France and England are quite dissimilar, there is a fair uniformity in the results. The determinations of chloroform in the blood, made by M. Nicloux, St. Martin, J. Mansion, and Tissot, depend upon the titration of the chloroform as chlorides, which are obtained from the blood by distillation with alcohol, rendered

acid with tartaric acid, and subsequent saponification with alcoholic soda or potash. The end point of the reaction is a colour one, yellow potassium chromate changing to an orange-red silver chromate. Buckmaster and Gardner have criticised this method, not adversely or unfairly; but it was incumbent to do this, since Nicloux in particular, who has performed much work by this method, regards it as a very exact chemical procedure, and he also believes that results obtained by methods other than this one are too high.

The principal results obtained by the French observers J. Tissot,[1] Mansion,[2] and Maurice Nicloux[3] are described at length in a recent paper.[4] The last observer found that the anæsthetic amount varied for different individual dogs. The same is true for the lethal amount, and the differences between the amount required to produce an anæsthesia in which all reflexes are abolished and the lethal quantity are small. He also found that the quantity of chloroform present in the blood at the anæsthetic stage was almost constant, and independent of the weight of the animal—a conclusion really equivalent to the view that the quantity of blood in the individual does not modify the percentage of chloroform in the blood. Tissot's observations were also carried out on dogs, and the method for determining the amount of chloroform in the blood resembled that employed by Nicloux. The results of Tissot's work showed that anæsthesia can exist with a very low chloroform-content in the blood, and that the amounts in arterial and venous blood differ. During the administration of chloroform the amount in arterial exceeds that in venous blood; during recovery from narcosis more of the drug will be present in venous than in arterial blood. Tissot lays special stress on the point that when mortal syncope or failure of the heart-beat is produced in dogs with a prolonged administration of low percentages of chloroform, comparatively large amounts of the drug are found in arterial blood; but just before actual syncope occurs the amount falls in a marked degree. From this fact he concludes that this diminution in the blood, which is a constant phenomenon, is

[1] *Comptes rendus de la Soc. de Biol.*, 1906, pp. 195, 198, 200, 203.

[2] *Ibid.* No. 4, 1906, pp. 206, 238, 241.

[3] *Ibid.* No. 2, No. 3, No. 7, 1906, and November 2, 1907, p. 391.

[4] "The anæsthetic and lethal quantity of chloroform in the blood of animals," by G. A. Buckmaster and J. A. Gardner, *Proc. Royal Soc.*, vol. lxxviii. 1906.

accounted for by an excessive exit of chloroform from the blood into the tissues of the body, and especially the brain. On this fact Tissot lays particular stress. It is clear, assuming that the experimental data are beyond question, that the cause of death must be ascribed not to a gradual process by which a slow, progressive toxic stage is reached, but to a somewhat sudden change, due to a rush of chloroform from the blood into the body cells; and if this occurs, it will become necessary for us to modify our entire views as to the whole process of anæsthetisation: for other experimental evidence, some of which has been already given, indicates that, with a definite pressure of chloroform in the blood, a definite constant effect is exerted upon the cells of the body. These cannot and do not take up indefinite quantities of chloroform; they take it up in response to a definite solution pressure which exists in the circulating liquids of the body. This remarkable drop in the chloroform-content of the blood we have not observed, though, in view of Tissot's work, the possibility that it might occur was especially considered.

The method pursued by Buckmaster and Gardner in their experiments was as follows: In all cases the percentage of chloroform vapour in the inspired air was determined for each separate experiment. The amount of chloroform in the blood was estimated by the difference in chlorine-content of the blood before the administration of chloroform, and again at any subsequent period from the time when the chloroform-and-air mixture was inhaled. The destiny of inhaled chloroform is traced by its chlorine, and the blood during anæsthesia contains an excess of this element. Numerous control experiments were made in order to ascertain whether the percentage of chlorine normally present in the blood of an animal remains sufficiently constant during a prolonged experiment. This was found to be the case when ether was the anæsthetic used. Small amounts of blood withdrawn from time to time during such an experiment were also found to in no way affect the percentage of normal chlorine in blood. The chlorine was estimated by the method of Carius, which is the one generally used for the determination of iodine, chlorine, or bromine in organic compounds. A known weight of blood, about three to five grammes, is treated with nitric acid, and an excess of solid silver nitrate in a bomb tube heated to 200° C. for six hours. The amount of resulting silver chloride was then determined, and the difference

between the chlorine-content of the blood before and after anæsthetisation with chloroform was calculated, and this gave a figure which could be expressed as chloroform. The whole method is an entirely new one, and has never been employed by earlier observers. In exactness it is believed to be preferable to those methods where the determination is a volumetric one with an end point which depends upon a colour reaction. Most of these experiments have been carried out on cats, while other observers have generally carried out their investigations on dogs. The chief conclusions arrived at were that the amount of chloroform in arterial blood at the moment when some definite reflex action disappears varies with different individuals. The same is true for the lethal amount in the blood; but a consideration of all the experiments taken together shows that only a narrow margin exists between the weight of chloroform in the blood at the moment of anæsthesia (loss of conjunctival reflexes) and the cessation of respiration (lethal amount).

The above outlines the methods of investigation, and enables the conclusions to be represented in the following table:

Observer.	Animal.	Anæsthetic amount of $CHCl_3$.	Lethal amount of $CHCl_3$.
Gréhant and Quinquaud, 1883.	dogs	50 mg.	...
Pohl, 1890. . . .	„	18–50 mg.	35 mg.
Nicloux, 1906 . . .	„	50 „	41–70 mg.
Tissot, 1906 . . .	„	34–40 „	60–105 „
J. Mansion and J. Tissot, 1906.	„	29 „	...
		32–43 „	...
Buckmaster and Gardner, 1906.	„	16–31 „ reflexes just gone .	61–69 mg.
Buckmaster and Gardner, 1906.	cats	14–27·5 mg. reflexes just gone	40 „

From these figures, which are in fair agreement, especially for the lethal dose, it would seem that the quantity of chloroform required to produce various stages of anæsthesia are somewhat higher in dogs than in cats. The difference, however, is not great. The lethal point is fixed as that at which the respiration is of a convulsive type owing to the onset of asphyxia.

The Rate of Assumption of Chloroform by the Blood

It is a familiar fact that when chloroform is inhaled the respirations may rapidly diminish in depth and frequency, or even actually stop within a few minutes. In the case of cats

it is exceedingly rare not to see this effect on a respiratory tracing. Any individual animal may exhibit this phenomenon in different degrees, and cessation of respiration may be permanent unless resort is had to some means of artificial respiration. Still more interesting is the fact that when the same animal is anæsthetised several times with the same percentage of chloroform vapour, this condition, which may be considered to indicate the first danger point in chloroform anæsthesia, occurs at the same time, and presents a constant type of impaired respiration. During this early period, in about two to three minutes after the administration of chloroform has commenced, a veritable danger point exists, and an elementary account of the physiology of this will be briefly described.

Nicloux points out that during this pre-anæsthetic period the intake of chloroform is rapid even with a low percentage of chloroform in the inspired air. Thus, within three minutes, 56 mgrs. per cent., an amount not much below the lethal quantity, were found in arterial blood when a somewhat large amount of the anæsthetic was supplied. Mansion and Tissot found that when a 4 per cent. chloroform-air mixture is inhaled, arterial blood becomes slowly but steadily charged with chloroform until the content of the drug in the blood is almost identical with the amount of vapour which it can hold *in vitro*. This is about 45 mgr. per 100 grammes of blood for an atmosphere containing 4 per cent. of chloroform (Tissot). After administration of this strength of chloroform, arterial blood contained the following amounts:

After . .	1 hr. 42 m.	1 hr. 50 m.	5 hrs. 15 m.	6 hrs. 56 m.	8 hrs. 21 m.
Mgrs. $CHCl_3$	27	30·5	36·7	42·4	46·2

In the experiments of Brodie and Widdows[1] the rate of absorption of chloroform during the introduction of anæsthesia was ascertained by allowing animals to inhale a known percentage strength of chloroform vapour, 1·06–2·78 per cent. Both the volume of air expired during any interval of time and the percentage of chloroform in this were determined, the latter by the same method which Vernon Harcourt had adopted, which depended upon the combustion of chloroform

[1] *Brit. Med. Journal*, July 14, 1906.

to hydrochloric acid. The chief new facts elicited by this work show, as might have been anticipated, that the rate at which chloroform is absorbed varies directly with the extent to which the lungs are ventilated. The slow and shallow respirations which occur so early in chloroform anæsthesia also stand in relation with a maximal retention of chloroform in the body, but how much of this is actually in the blood could not be stated. It is, however, abundantly clear that the minimum amount of chloroform in the expired air is found during the second minute, and from that period onwards the amount escaping from the body slowly rises. In a series of experiments, each lasting ten minutes, it was also observed that the amount of chloroform absorbed increased with the concentration of the drug in the inspired air, but the amount was not in proportion to the concentration.

In the experiments of Buckmaster and Gardner,[1] which were carried out on cats, small quantities of blood were withdrawn from time to time from an artery during the induction of anæsthesia with known percentages of chloroform vapour and air. The determination of the quantity of chloroform in these samples, ten or twelve in each experiment, afforded the data from which curves could be constructed. In all of the curves the same general features were seen. In the pre-anæsthetic period, or initial stages of anæsthesia, at a time when the individual is conscious, the chloroform-content of the blood rises with great rapidity to a value which approaches a maximum. During this period, which occupies the first few minutes, the first danger point in anæsthesia occurs, because the quantity of chloroform in the blood directly or indirectly affects the respiratory nerve-centres of the brain. In consequence of the respirations being slower and shallower, the amount of chloroform in the blood falls, but the fall is also due to the exit of the drug from the blood into the tissue-cells of the body. When the animal has passed this first stage the amount of chloroform again quickly rises towards a maximum value, and an equilibrium between the factors which determine the amount of chloroform in the blood appears to be obtained, the processes of intake and output of the anæsthetic at the surface of the lung going on side by side. In other words, a state of equilibrium is reached, which persists for a considerable period, and throughout this period the difference

[1] *Proc. Royal Soc.*, B, vol. lxxix. 1907.

between the amount of chloroform present in the blood and what is found at the lethal point is very minute. The state is far from one of safety, and the animal may suddenly die at any moment should any disturbing factors come into play. The whole of this period is a danger period. In the experiments quoted the percentage of inspired chloroform was maintained constant, but it is evident that the contention of those anæsthetists who have insisted that after anæsthesia has been established this can be and should be maintained with a much smaller amount of chloroform vapour, rests upon a sound basis.

Space does not allow of more than a reference to the heart failure which may occur in chloroform narcosis. An inhibition of this organ to such an extent that no blood can be driven through its chambers, though the heart is still beating, may occur at the first danger point of anæsthesia. Particularly valuable work in connection with this has been carried out by Embley,[1] Leonard Hill,[2] and by Brodie and Russell.[3] Studied from the point of view of a reflex action, the last observers have shown that a very close relationship exists between the respiratory tract and those nerve-centres of the brain which control the heart-beat, the respiratory movements, and the bore of the small arteries in the body. The most sensitive surface which, when stimulated, reflexly affect these centres is that of the lining of the nose, next the mucous lining of the larynx, and then the surface of the lungs, which are powerfully stimulated by vapours of chloroform, formaldehyde, and bromine. When the internal surfaces of the trachea and bronchi are irritated no reflex of the type just described can be evoked. Stopping of the heart alone is very easily brought about as a reflex action by stimulating the pulmonary branches of the vagus. The experiments of Embley have shown that for dogs the first danger point, cardiac inhibition, and consequent slowing of the respirations, can be entirely set aside by removal of the heart from the influence of the centres in the brain by cutting the two vagi nerves along which the impulses which check or arrest the heart normally pass. The effect of atropin, which cuts out the inhibitory influence of the vagus upon the heart, has been re-investigated by Schäfer

[1] *British Medical Journal*, April 5, 12, and 19, 1902.
[2] *Ibid.*, April 17, 1897, and December 1900.
[3] *Journal of Physiology*, xxvi. 1900.

and Scharlieb,[1] who have suggested its employment prior to chloroform anæsthesia. Embley and F. J. Martin[2] have also demonstrated the toxic effect of chloroform upon the unstriped muscle in the walls of the blood-vessels. These dilate when perfused with blood charged with a small percentage of the drug.

The Function of the Red Corpuscles in Chloroform Anæsthesia

Schmiedeberg was of opinion that the red corpuscles were the chief vehicles in the transport of chloroform from the lungs. This was supported by Pohl's experiments, and Nicloux, who used centrifugalised oxalated blood removed from a vein, recovered 64·4 per cent. of the chloroform in blood from the red corpuscles and 13·3 per cent. from the plasma. His figures for the distribution of chloroform among the constituents of the blood are much below those of Pohl, who had stated that 87-90 per cent. of the total chloroform was held by the red corpuscles; in other words, the chloroform-holding power of the corpuscles is seven to eight times that of the plasma.

Experiments undertaken by Buckmaster and Gardner, in order to ascertain how the anæsthetic distributes itself in the blood between the corpuscles and plasma, proved to be exceptionally difficult.[3] The separation of the corpuscles was accomplished by centrifugalising tubes of blood surrounded with ice, so as to hinder any clotting. Their conclusions, that chloroform is very firmly held by the blood of an anæsthetised animal, are in accord with all other observers. But it was also found that chloroform primarily associates itself with the red corpuscles and does not enter the plasma to any marked extent unless the anæsthesia is pushed to an extreme degree, or a chloroform-and-air mixture is administered with a high percentage of the drug. At the period when the reflexes disappeared the percentage of chloroform in the red corpuscles was found to be 64·3 per cent.; in another case 71·1 per cent., and after the inhalation of 2 per cent. chloroform for three quarters of an hour no less than 98·5 per cent. of the anæsthetic was held by the red corpuscles.

[1] *Trans. Roy. Soc. of Edinburgh*, vol. xli. Part II. (No. 12).
[2] *Journal of Physiology*, xxxiii. 1905.
[3] *Proc. Royal Soc.*, B., vol. lxxix. 1907, p. 566.

In order to obtain additional proof that the red corpuscles, as would seem to be the case from the above experiments, are the essential vehicles for the carriage of chloroform, Buckmaster and Gardner argued that if the view was correct that the transport of chloroform was a function of the red corpuscles, then, though the absolute amount of chloroform present in the blood might be modified by abstracting or adding blood from or to an animal, the *percentage of chloroform* ought to remain constant.

The general plan of the experiments was to anæsthetise an animal with ether or nitrous oxide, allow the anæsthetic to be disengaged from the body, and then administer a known percentage of chloroform. The determination of the amount of the drug in the blood was made at the asphyxial point. In one hour or an hour and a half all the anæsthetic was eliminated, and during this period a measured amount of blood was abstracted and the experiment repeated. In other experiments the amount of chloroform present was determined in the same animal before hæmorrhage, after hæmorrhage, and after the replacement of the blood which was furnished from another animal in such quantity as to augment the original volume of the blood by one-third to one-half.

The general results of all the experiments will now be detailed.

	Average amount of $CHCl_3$ per 100 grammes of blood.	
	Before bleeding.	After bleeding.
Experiments in which the asphyxial state was rapidly reached, in about 3 to 9 min.	0·043 mg.	0·045 mg.
Experiments in which the asphyxial state occurred in about 30 to 80 min.	0·048 „	0·051 „

	After hæmorrhage.	After replacement of the blood.
Experiments made at the asphyxial point.	0·0421 mg.	0·0426 mg.
	0·0768 „	0·0768 „

	Before hæmorrhage.	After hæmorrhage.	After replacement of blood.
Experiments made at the asphyxial point.	0·061 mg.	0·059 mg.	0·049 mg.

From the above it would appear that the conclusion is justified that the percentage of chloroform in the blood does not undergo any variation corresponding to differences in the

volume of the circulating blood, and this is what was to have been expected if the red corpuscles were the essential agents for the transport of chloroform. It may be considered in the highest degree probable that the anæsthetic is associated with the proteins of the corpuscle, but the experiments naturally give no clue as to whether it is the hæmoglobin or other cell-proteins which actually pick up the drug. The earlier work of Hedin, Overton, G. W. Stewart, and Oker Blom, among others, on the permeability of the red corpuscles is of considerable importance in connection with the association of chloroform by the corpuscles. Stewart has pointed out that as far as certain electrolytes are concerned the permeability of the envelope alone, or of the whole disc, is dependent not on the life but on the structure of the corpuscles, for these, under a variety of conditions which are incompatible with life, and when the hæmoglobin is converted into methæmoglobin, preserve their permeability to some substances, but remain relatively impermeable to the electrolytes of the plasma. Hedin's experiments have demonstrated that some substances, such as sugar or sodium chloride, are unable to penetrate the corpuscles, while substances like urea, antipyrin, and the narcotic urethane easily enter them. The group of aldehydes, ketones, and alcohols, many of which affect the organism like the better known anæsthetics, if added to blood are found to be so distributed that nearly all the added substance is found in the red corpuscles. The significance of such experiments is great, for it establishes the fact that alcohol, or a narcotic, like urethane, can, and actually does, enter the cells of the body.

The Rate at which Chloroform is eliminated from the Blood after Anæsthesia

All observers are agreed that after the supply of chloroform is stopped the anæsthetic rapidly leaves the body. Five minutes after anæsthesia half the amount in the blood had disappeared; 7 milligrammes were found three hours later, and by the seventh hour the blood became free from chloroform (Nicloux). Tissot suggests that a study of the amount of chloroform in arterial blood should be made during the induction of anæsthesia, but that determinations of the chloroform-content of venous blood are necessary if we are rightly

to understand the rate at which it is eliminated. According to his experiments, the amount of the drug in venous blood constantly exceeds that in arterial during recovery from chloroform narcosis. Expressed in other words, directly the administration of the anæsthetic ceases the cells of the body begin to discharge their associated chloroform, and with this their functions gradually become restored. The subjoined table from one of Tissot's papers is of interest:

	Milligrammes of $CHCl_3$ per 100 grammes of blood.		
	Chloroform administration stopped.	45 min. later	2 hr. later.
Arterial blood . . .	53·2	5·8	0
Venous blood . . .	48·1	7·7	4·9

In our own experiments,[1] immediately the inhalation of chloroform stopped, a sample of blood was taken from an artery, and this was repeated at intervals, until half or three-quarters of an hour had elapsed. In other experiments venous blood taken close to the right ventricle of the heart was examined in the same way, while in a few experiments samples of arterial and venous blood were taken simultaneously. The main conclusion which can be drawn from these experiments is that the rate of elimination of the drug from the body *viâ* the blood depends upon the physiological state of the individual animal. The rate of loss is at first comparatively rapid, and subsequently becomes slower. But the initial rates of elimination are much less rapid than the initial rates of the intake of chloroform, and, on the whole, elimination is a much slower process than assumption, a view which is supported not only by the actual determinations of chloroform in the blood but by a comparison of the times at which the various reflexes disappear and reappear. From our curves the initial falls are not quite so rapid as the work of other observers had led us to suppose. The chloroform-content of the blood was only reduced by 50 per cent. in 15 to 20 minutes; three-quarters of the chloroform was eliminated in about half an hour. These statements hold good when the animal is breathing naturally, but, as might have been expected, the extent to which the lung is being ventilated during any period is the chief, if not the only, factor which determines the rate of elimination. Our experiments are in

[1] Buckmaster and Gardner, *Proc. Roy. Soc.*, B., vol. lxxix. 1907.

agreement with Tissot's observations, that at the moment when chloroform inhalation stops arterial blood contains an excess of the drug when compared with venous blood, but the difference between the amount of chloroform in arterial and venous blood after regular respiration is established is practically the same.

A sufficient and satisfactory explanation of the anæsthetic process probably cannot be given at present, but some conception of the anæsthetic state produced by the inhalation of chloroform vapour at about 2 per cent. may be attempted. It is true that data for this have been obtained by experiments on cats, but it is allowed that the phenomena shown by this animal during anæsthetisation closely resemble what is seen in man. The blood at first rapidly becomes charged with chloroform, which is held almost entirely by a protein or proteins of the red corpuscles. The respiratory centre or centres are at first stimulated, but these become affected quite early, and then discharge pulses less frequently and less efficiently than in a normal animal. In the dog especially, and to a less extent apparently in the cat, this behaviour of the centre is secondary to a weakening, or almost a cessation, of the activity of the heart. From this inhibitory effect the heart escapes, somewhat easily in the cat compared with the dog. The condition just described occurs early, within the second to the fifth minute, and may be considered as the first danger point in anæsthesia. In consequence of the slow and shallow respirations, the percentage of chloroform in the blood falls, either owing to a diminished intake of vapour or to the cells of the body storing up the drug at the expense of the blood, or because the elimination of the drug is as rapid, or more rapid, than the assumption. But the last cannot be the explanation, for the rate of elimination is by no means so rapid as is the assumption. The fall is, therefore, due largely to the disappearance of chloroform into the cells of the body, which, in virtue of their proteins, are capable of forming loose chemical combinations or aggregations with the drug. The cells are, in consequence, poisoned in varying degree. When the first danger point is safely passed, the respiratory movements improve in frequency and vigour, and this may be considered to represent a continuation of the initial stimulating effect of the drug, which was masked by the occurrence of a danger point. Thereafter the chloroform-

content of the blood quickly approximates to a maximal value, which is maintained until asphyxial convulsions occur. This may be termed the second danger period. The difference between the chloroform-content of the blood at the initial period, when the first danger point is reached, and also at the maximal value, when compared with the lethal amount, is very minute. The quantity of the drug in the blood governs the distribution of the anæsthetic which at first stimulates, and then finally paralyses certain cell districts of the body in definite order. Chloroform, therefore, though a toxic substance, does not produce its effects upon the organism by a cumulative action; these are not dependent upon the absolute quantity which is supplied, but upon the percentage-value of the drug in the blood stream.

THE REFORM OF THE MEDICAL CURRICULUM (II)

By PROFESSOR HENRY E. ARMSTRONG

Another act in the drama of medical education was recently played to a finish when the Senate of the University of London, at its November meeting, decided that it was unable to evolve a constructive scheme which would render possible the use of the great gift offered for the establishment of a school of preliminary medical studies at South Kensington. Like the truth, jealousy has prevailed: London seems to be ever at the mercy of contending factions—a natural result, perhaps, as she altogether lacks leadership.

I am constrained therefore to continue the article on the reform of the medical curriculum which I contributed a little more than a year ago to this journal and which, meanwhile, has met with a rejoinder from Dr. Wade (No. 4, April 1907).

Dr. Wade and I are obviously looking at things from different points of view: his being that we are living under almost ideal conditions, which cannot well be changed and which need not be changed; mine that we are in a time of makeshift: that it is our duty to take stock of the situation, to mend our ways without delay. Thinking that all is for the best in the best of possible worlds, he would pursue a *laissez-faire* policy. My desire is to see a new point of view introduced into the subject: it seems to me that it is useless to attempt to teach chemistry to medical students except as the study of function—the study of processes. Unless they can more or less understand the nature of the chemical processes which occur normally and under pathological conditions, as well as in some measure appreciate the alterations likely to be effected by changes in the conditions, they cannot possibly penetrate behind the veil which Nature at present draws in front of them.

I believe medical opinion will be with me; that many will agree with me that the preliminary studies, as at present conducted,

afford neither systematic scientific training nor proper technical training, the memory being merely loaded with a vast mass of uncorrelated facts, some of which, of course, are of interest and value: in the main, however, the time spent in acquiring them is ill spent, as a false direction is given to the mental activities. To give an example—happening recently to mention *Cholesterol* to a sharp young medical student now following the clinical course, I met with the pat reply—"Oh yes, that is the stuff in Lanolin: a monatomic alcohol, crystallising in rhombic plates with a bit snipped out of one corner, which gives a fluorescent red coloration with strong sulphuric acid." "Knowing that," said I, in amusement, "you must feel that there is nothing more to be learnt on the subject and that you are provided for life with information of inestimable value." "With information," said he, "sufficient probably to make the difference between passing or failing in the Second M.B." (at Cambridge). This illustrates, not inaptly, the present-day attitude, the kind of knowledge which it is thought is essential —and which is taught as essential.

It is worth while to examine Dr. Wade's case somewhat in detail. In discussing my qualifications to act as critic, he implies that I have taken an interest only in elementary school affairs and pictures me as a sort of educational Rip van Winkle, returned to the scene of my early labours with rusted barrel and decayed stock, unable to divest myself of old memories—thinking only of medical education as it was in the days when I took some direct part in it: the days of blackboard demonstration without practical illustration. I can scarcely think of myself as so entirely decadent. Like that contraption the Tar Baby, I may have worn the appearance of a mere scarecrow in medical eyes. Brer Wade forgets, however, that it is possible to lie low with eyes open; like Brer Rabbit, to take notice of all kinds o' persons, keeping the old woman at hand watching the kettle on the fire, in readiness when the time comes to pour down the "bilin" water on Brer Wade and his friends, practice having been gained meanwhile by spilling some of it on schoolmasters' heads.

Feeling as I always have and still do that a solid foundation is the first requisite, I have done my best to promote the introduction into schools of teaching calculated to develop some understanding of scientific method. Some little progress has

been made and in the last years of the old University of London, partly perhaps owing to my representations, some pressure was being brought to bear on the schools to make such teaching rational and effective. One of the first acts of the newly constituted University—one of its most retrograde and unforgivable acts—was to undo the good work of its predecessor. The protests made by those of us who had experience of the value of the system under which some knowledge of science was required of all at Matriculation were unheeded; we were advisedly excluded from all Committees dealing with such matters, and freedom to neglect their duty was conferred upon the schools preparing candidates for matriculation. Freedom, we all admit, is good in the abstract—but freedom is easily abused by those who are not ripe to enjoy it: for the most part, the schools were incapable of running alone—they were and still are in need of guidance.

Men like Dr. Wade apparently do not realise the truth of the adage that there are more ways of killing a pig than sticking it—that it is policy sometimes in hunting to approach your quarry in indirect ways—that there may easily be more haste and less speed—that it is well sometimes to play a waiting game, to exercise purpose silently. His present experience as a teacher of medical students is not very much greater than mine was when I gave up such work; since then I have been steadily engaged, I regret to say during five-and-twenty years, in educational research work—constantly making experiments, constantly thinking over and discussing the problems of education. My wits have been sharpened the more in that I have enjoyed an opportunity which has fallen, I think, to no other teacher of chemistry quite in the same degree—that of developing courses for and ministering to the wants of large special classes of students not destined to follow a chemical career, engineers mostly, first at the Finsbury Technical College, then at the Central Technical College. This more than anything else has led me to appreciate the possibility of teaching a subject in relation to its technical uses. I venture therefore to suggest that Rip has been active in retirement, not asleep; that he is down from the mountains by no means unfit for the fray.

And in other ways the course events have taken has been such as to impress me with a sense of the gravity of the

situation. But a few months after I commenced to breathe an atmosphere of apomorphine[1] at St. Bartholomew's Hospital Medical School in 1870, my chief Matthiessen came to an untimely end. I discovered him, one afternoon, asleep for ever, in his armchair: my first experience of real life—in itself an event to make a young man think. Had he lived, Barts might well have been made the centre of research on alkaloids and their use in medicine, a centre of inspiration—as he was a man of indomitable energy, full of scientific enthusiasm, with an extraordinary faculty of choosing workers and making them work; he had too the gift of insight and was interested in things organic and inorganic; in fact, he was a complete chemist in feeling: one who could determine electrical conductivities without lapsing into ionomania and who would have set his face against unreal, pretentious talk on the subject. His work on narcotine with Carey Foster and Alder Wright practically laid the foundations of alkaloidal chemistry. Whenever a chance comes to us in this country, however, we seem to let it lapse: lack of scientific training and of the scientific spirit has led the medical profession to overlook the advantages accruing from systematic research work, and the development of a narrow humanitarian spirit among the public now threatens to put a complete stop to such work in medical schools, as the hospitals are held to exist solely for the cure of poor patients: the number of persons, poor and rich, is in no way thought of who die lingering deaths because of our neglect to carry on systematic inquiry in directions likely to be of benefit to medicine. The chance once in the hands of Barts, thoughtlessly sacrificed, will not soon occur again, I fear.

In my former article, I spoke of a just feeling among medical men "that the present course in chemistry is a totally unfit preparation for medical practice"—and added: "this is the feeling we have to meet and provide for." Dr. Wade notwithstanding, I still affirm this to be the case, and I have reason to think that the teaching of other preliminary subjects is more or less open to similar criticism.

He has represented me as having made "an attack" on the curriculum of the University of London—in reality, my remarks

[1] Apomorphine was then under investigation and was in the air in more senses than one.

were of general application, the condition of schools outside London being at least as unsatisfactory as that of those in London.

I have led the reader who is unacquainted with the subject to believe, it appears, that medical education has remained unaffected by the rapid march of science during the past fifty years—actually I drew attention to the many improvements effected even during my time.

My remarks, Dr. Wade considers, might lead readers to believe that our whole system is radically wrong—they were intended to have that effect.

That the issue will be fraught with disaster unless the curriculum is remodelled, I have no doubt: it is already, in fact. Men are dying on every side owing to our inability to apply chemical knowledge to the interpretation of disease. Such homicide, however unwilful, must none the less come to be regarded as unjustifiable, if a consequence of ignorance which it is in our power to overcome. And it is in our power to overcome it, at least partially.

A stern duty may also lie before medical men for which they will have to be prepared. Many are living whose existence perhaps is a matter of extreme danger to the State, as the perpetuation of their kind may be expected to have the most serious consequences. The problems of heredity need consideration from this point of view; unless medical men can undertake their study and act as advisers of the public, society will not receive that protection which sooner or later it will come to expect from the medical profession.

Although surgeons have advanced their practice by leaps and bounds, that of medical men has almost stood still: the great improvements—such as the treatment of rabies and diphtheria by appropriate antitoxins and the various new potent drugs, not forgetting lumbar anæsthetics—are due to chemists. The fact is the medical man is not sufficiently versed in scientific method to undertake the diagnosis of the obscure phenomena of chemical change in the complex material which constitutes the human body. He understands but few simple chemical changes occurring in test tubes—the complexities of change under vital conditions are entirely beyond his ken and grasp.

The case is well stated by Archdall Reid in the following passage (*The Principles of Heredity*, 2nd ed. 325):

The principal aim of that part of formal education which is not specially intended to supply the individual with useful knowledge should be to develop his reflective powers. Much scientific teaching as practised at present does not fulfil this condition. For example, the medical profession includes the largest number of scientific men in the world. From first to last during his career the medical student is loaded with a monstrous and ever-increasing burden of facts, but no systematic effort is made to increase the acuteness and range of his thinking processes. A great deal of the burden on his memory is necessary ; but not all of it. Thus since he treats the ailments of an animal, man, largely by means of vegetable drugs, he is taught botany and zoology. In botany he learns such things as the peculiarities which distinguish various natural orders of plants from other natural orders. In zoology he acquires a more or less elaborate knowledge of the structure of certain types of animals—the vascular system of the sea-urchin, the organs of generation of the earthworm, the skeleton of the frog, the bones of the cod's head, the dentition of the different species of mammals and so forth. But no man is a better physician for knowing the difference between a raceme and a rhizome, nor a better surgeon because he has studied the anatomy of the cockchafer. His subsequent experiences do not link up with these fragments of knowledge which, though necessary to the equipment of the professional botanist and naturalist, are so remote from the labours and interests of the medical career that presently they are forgotten. In the end the average doctor has a knowledge of botany and zoology not much more profound nor useful intellectually than that possessed by the average farmer or stockbreeder. Either he should be otherwise employed during his earlier studies or his later work should be so modified as to link up with them. Facts, scientific or other, have by themselves no intellectual or scientific value. It is the recognition of the relationship between facts in a natural group and between different groups that confers the value. No doubt medical students, in proportion to their intelligence, get a general notion of the essential likenesses, which, amid distinguishing differences, bind together all living nature. But this result, if it be the one sought, is attainable by direct teaching at a hundredth part of the cost in time and labour.

It is the misfortune of the public as well as of the medical man that he is placed in this position. And to him before all others it is of importance to remove the disability from which his profession undoubtedly suffers. He can help more than most if he care to act—as there can be little doubt that the public would be advised by him. The clergy no longer count in education—as a body they have ceased to take an interest in the subject, and their interests are thought to be so opposed to those of the modern scientific school that they are not likely to intervene on behalf of training the value of which they are entirely unable to appreciate. It is the more important, therefore, that medical men should recover the position they formerly held in common with the clergy, as men of culture.

In defending myself against the charge of being asleep—as Dr. Wade suggests that my allegations are vitiated by inability

to divest myself of old memories—I may not unfairly point out, perhaps, that my critic is not yet awake to possibilities which I seem to see clearly. His conservative attitude is in itself proof that he is scarcely qualified to enter on a discussion such as we are now engaged in. His connection with the subject of medical training arises rather from his being in a medical school than of it. Apart from his obvious lack of feeling on the physiological side, in common with so many other chemists he in no way realises apparently how vast is the change which has come over chemistry within recent years, making it possible to teach the subject far more effectively than formerly. Herein lies the difficulty. Our brains are addled by the constantly increasing load with which we weight ourselves. Very few can see their way out of the wood for the trees. We do not even know how to use books effectively and insist on our students learning off everything by heart instead of teaching them to understand principles and economise effort by referring to their books for detailed information when occasion arises.

Dr. Wade argues that the teaching is enormously improved. Formerly, he says, the scientific spirit was absolutely destroyed by blackboard demonstrations without experimental illustrations and no opportunity was given to the student of verifying his teachers' statements: it is quite otherwise now. Is it? Does the average student gain much from seeing a few practical demonstrations in the course of a lecture or from preparing a few substances in the laboratory? I doubt it. The intelligent man in the old days learnt from lectures practically as much of things essential as the intelligent man does in these days: then as now far too much attention was paid to mere fact knowledge, to the kind of fact which comes into prominence, for example, in Dr. Wade's own book—of its kind, a very admirable one—or as illustrated above by the reference of my young student friend to cholesterol. The one real improvement in the course is the introduction of simple quantitative laboratory work, such as I pleaded for in my B.A. address in 1885—conceptions are established in the mind of the student by such work which are invaluable.

Instead of dealing with irrelevant matter, says Dr. Wade, the proximate constituents of the food, degradation products of the body, urea, etc., are considered. The same were dealt

with in my day. The question is—How are they dealt with—any more usefully than formerly? I doubt it. Murder will out, and out it comes when Dr. Wade tells us that "Chemistry for medical students bears precisely the same relation to physiology and pathology as anatomy does, the chemist dealing with the nature and relation of the materials and the anatomist with the nature and relation of the structures the function of which, in both cases, it is the part of the physiologist to investigate." Chemistry as thus defined by Dr. Wade is a kind of dry-bones business—and so it usually is; the chemistry the medical man needs, however, is not for the most part anatomical but functional: physiology, therefore, in a large measure, overlaps it. This is what Dr. Wade and his friends do not see—but they must come to recognise it, sooner or later.

Students, in his laboratory, says Dr. Wade, dissect chemically and, where possible, reconstruct artificially, compounds such as urea. Suppose they do—how much better off are they? As ordinarily conducted, the exercise is an almost worthless one, in my opinion. And from a medical point of view, it doesn't really matter what urea is: a harmless waste product, containing oxygen and nitrogen in their lamest form, its importance is generally much overestimated in chemical circles, just as we now have reason to suppose it was by Fick and Wislicenus, who spent much unnecessary effort on the Faulhorn in worship of its supposed functional significance. The student does not really dissect it when he gets ammonia, etc., from it any more than an anatomist dissects a bone when he gets calcium phosphate from it; probably, moreover, urea is not what he is commonly taught to suppose it is—*carbamide.* Long absorbing conversations which I had with Peter Griess—the prince of nitrogen chemists—in days of yore rise in my memory when I write this: he would not listen to its being called carbamide.

The really important problems centring around urea are not taught—the wonderful inter-relationship of the closely allied forms of the compound CON_2H_4; the condition of equilibrium in which urea, carbamide and ammonium cyanate subsist in solution: although probably of high physiological importance, these subjects are considered to be far too difficult for the medical student to tackle; really they are the points which he should be led to study very thoroughly. From the medical point of view, the substances which accompany urea

in urine in fluctuating proportions are far the more important —as they are often of diagnostic value.

If those to whom I am addressing myself scarcely grasp the force of this argument, they will nevertheless see, assuming my contention to be correct, that the suggestion that chemistry is taught in medical schools in an unsympathetic manner cannot be so far from the truth after all!

Dr. Wade altogether objects to the proposition that we might well give some consideration in the first instance to complex cases, such as the processes of digestion, for example. From the objection he makes, it is clear that he in no way appreciates the marvellous advance made in this field of late years. Knowing as we do now the fundamental importance of enzymic action both in up-grade and down-grade processes, it is clearly our duty to make this a primary subject of study. Colloid substances also invite special attention and such simple substances as water, which now is scarcely considered, although physiologically perhaps the most important constituent of the body; what is taught about it—its composition, etc.—is worthless for all practical purposes.

According to Dr. Wade, present-day examinations in science are very different from and better than those held when I taught medical students. They are absolutely the same, except—and the improvement is a real one—that simple quantitative exercises have been introduced into the practical chemistry examinations. When I contrast the questions set last year with those set twenty-five years ago, I find no difference: the same stock academic riddles are propounded year after year. At no time have the questions had any real bearing on the problems which face the medical man; those set during the past year or two are as futile as those which I assisted in setting in the early 'nineties, although meanwhile, as already pointed out, there has been a vast development of knowledge.

The main lines on which chemical change proceeds having been made clear to us, there is no question that it is now possible to teach a chemistry which should give eyes to the medical man and enable him gradually to pierce the gloom which still enshrouds the subtler changes: I therefore contend that we are much behind the times.

Dr. Wade not only says that chemistry is now taught (in

the London Medical Schools) with direct reference to its scientific application in physiology and medicine, but that the curriculum laid down for medical students has been specially constructed and, except in the purely elementary parts, is essentially different from that laid down for chemical students. Let us see if this be so. I take the following first year's course of study from the Regulations (issued in September 1907) in the Faculty of Medicine for Internal Students:

Inorganic Chemistry

The *Curriculum* in Chemistry shall consist of not less than sixty Lectures and one hundred and twenty hours' Practical Work in the course of an Academic Year. The Syllabus is as follows:

I.—For Lectures

Illustrations and examples of chemical action. Solution, crystallisation, distillation, sublimation, precipitation. Mixtures and single substances, separation and decomposition.

Gaseous and liquid diffusion.

Indestructibility of matter. Elements and compounds. Laws and condition of chemical action.

The atomic theory. The determination of molecular weights, equivalents and atomic weights. Valency and structural formulæ. Equations. Chemical calculations.

Classification of the elements, including the periodic system. Synthetical production of compounds from their elements. The general characters of the chief types of compounds. Acids, bases and salts. Chemical nomenclature and terminology.

The principles of gravimetric and volumetric analysis.

Production and properties of the more important and typical elements and of their most familiar compounds.

The character of chemical changes, including the study of simple exothermic and endothermic reactions, thermal dissociation, electrolysis, catalysis, mass-action and rates of reaction; the conditions which determine and influence such changes and the attendant phenomena. Osmotic pressure.

The above to be illustrated by a detailed consideration of the following:

Oxygen, *Nitrogen*, *Hydrogen*.—Chemical nature of the atmosphere; composition and properties of water; natural waters; the oxides of nitrogen; nitrites and nitrates; ammonia, ammonium salts, hydroxylamine; hydrogen peroxide, ozone.

Carbon.—Its oxides, carbonates; relation of carbon dioxide to animal and plant life; carbon disulphide; coal and coal-gas; combustion; nature of flame; cyanogen, hydrocyanic acid and the metallic cyanides.

Fluorine, *Chlorine*, *Bromine*, *Iodine*.—Their compounds with hydrogen; oxides of chlorine, hypochlorites, hypobromites, chlorates, iodates.

Sulphur and Phosphorus.—Their compounds with oxygen and hydrogen; chlorides of phosphorus; sulphides, sulphates, sulphites, sodium thiosulphate; phosphates.

Boron and Silicon.—Their oxides; boric acid and borax; silicon fluoride; nature of glass.

Occurrence in nature, sources and preparation of the following metals and their principal compounds, omitting metallurgical processes: lithium, sodium, potassium; calcium, strontium, barium, magnesium, zinc, cadmium; copper, silver, mercury; iron, aluminium, chromium; manganese; lead, tin; arsenic, antimony, bismuth.

(N.B.—The whole subject will be treated in an elementary manner.)

II.—For Practical Work

The Course must be such as will enable Students—

(*a*) To prepare and demonstrate the properties of common metallic and non-metallic substances and to purify them by precipitation, crystallisation or distillation.

(*b*) To perform accurately the following simple quantitative operations: the determination of the equivalents of copper by reduction of its oxide and of copper, tin and zinc by oxidation; alkalimetry and acidimetry; the estimation of chlorides gravimetrically and by titration with silver nitrate; and determinations involving simple applications of the permanganate and iodine thiosulphate processes.

(*c*) To identify by simple tests the common elements and their more familiar compounds, including mixtures which may contain not more than one acid and two metals belonging to different analytical groups.

(*d*) To write out a clear account of their practical work, accurately describing the nature of the processes employed and, where possible, representing by equations the chemical changes involved.

To my thinking, the course here laid down is an ordinary, thoroughly old-fashioned and conventional preliminary course of inorganic chemistry. There is not a single word to indicate any connection with either physiology or medicine. It scarcely differs from the 1890 scheme, except in the practical part, *a* and *b* in this being new: (*b*) is admirable in principle: the improvement in teaching, to which Dr. Wade refers, in my opinion is due to its introduction; what (*a*) may or may not mean it is difficult to say.

The current scheme for chemistry in the Faculty of Engineering is as follows:

The methods which lead to the discovery of the composition of common materials occurring in nature.

The determination of molecular weights, equivalents and of atomic weights. Valency and structural formulæ.

Classification of the elements, including the Periodic Scheme.

General characters of the chief types of compounds, including acids, bases and salts and a few prominent carbon compounds, especially as illustrating the relations of properties to composition and structure. No distinction will be admitted between Organic and Inorganic Chemistry.

History, production and properties of the more important and typical elements and their most familar compounds.

The character of chemical changes, including combustion, thermal dissociation

and electrolysis; the conditions which determine and influence them and the attendant phenomena.

The whole to be treated in an elementary manner.

Tersely worded as it is, this is infinitely superior to the medical scheme as a statement; but it is essentially the same scheme; not essentially different from the latter. The fusion of organic with inorganic chemistry, which Dr. Wade speaks of as having been tried with disastrous results, is treated, it will be noticed, as an accomplished fact.

Passing to the second year's course, we have the following :—

The *Curriculum* in Organic Chemistry shall consist of not less than sixty Lectures and sixty hours' Practical Work in the course of an Academic Year.

The Syllabus is as follows :

I. For Lectures

1. Purification of solids and liquids.

2. Analysis of organic compounds. Estimation of carbon, hydrogen, nitrogen, sulphur, phosphorus and the halogens.

3. Empirical and molecular formulæ. Determination of molecular weights.

Students will be expected to know the general properties of the following groups of compounds, illustrated in each case by reference to a few of its more important members :

Aliphatic Series

Paraffins (especially methane and ethane).

Unsaturated hydrocarbons (especially ethylene and acetylene).

The different classes of alcohols and their derivatives (with special reference to methyl alcohol, ethyl alcohol, glycerol and mannitol).

Aldehydes (with special reference to formaldehyde, acetaldehyde and chloral hydrate).

Ketones (with special reference to acetone).

Acids (with special reference to formic, acetic, lactic, oxalic, succinic, malic, tartaric and citric acids).

The preparation and properties of the following derivatives of acetic acid : acetyl chloride, acetic anhydride and acetamide.

Simple ethers (with special reference to ethyl ether).

Esters (with special reference to ethyl acetate and saponification).

Amines. Amido-acids. Glycocoll.

Carbohydrates. Sugars (and more especially glucose, fructose, lactose, maltose and cane-sugar). Starches. Glucosides.

Cyanides. Urea. Uric acid.

Aromatic Series.

Hydrocarbons : benzene, toluene and their simple derivatives.

Sulphonic acids.

Phenols (with special reference to phenol, catechol, hydroquinone and resorcinol).

Benzyl alcohol. Benzaldehyde.

Acids. Benzoic acid. Salicylic acid.

Pyridine.

(N.B.—The whole subject will be treated in an elementary manner.)

In 1890, the Organic Intermediate course was as follows :

The composition, the properties and reactions and the more important derivatives of the following substances :

The principal series of Hydrocarbons (with special reference to their chief Haloid and Nitro-derivatives).

The Ethylic series (with special reference to ethers, esters or ethereal salts, aldehydes, ketones and acids).

Glycol. Glycerine ; natural fats.

Amylaceous and Saccharine substances.

Vegetable acids.

Benzene and Toluene with the principal Phenols and Nitro-derivatives.

Ammonias and the more important natural Alkaloids.

Amides, Urea, Uric Acid.

Cyanogen, Cyanides, Cyanates and Cyanurates. Glucosides.

The processes of Saponification and Fermentation.

The principles involved in Ultimate Organic Analysis and in the determination of Molecular Weight.

Again, the difference is merely nominal, except in the practical work, which is now slightly superior to the old pass but inferior to the old honours examination, as this included the volumetric Pharmacopœia work. It is noticeable that hydrolysis and fermentation could be examined on in 1890 but that the latter is now left out, although of infinite importance from a medical point of view. Evidence that the subject should be taught with direct reference to its scientific application in physiology and medicine can only be found in the entire absence of reference to this desirability. Indeed, with such syllabuses in operation, the authorities have no right to expect any special knowledge of medical applications from candidates—and the examination papers show that the examiners are either alive to this fact or are unable to deal with the medical aspects of the subject.

In the true school of the future, teachers will not be restrained by stereotyped syllabuses ; they will teach what is necessary without reference to any narrowing schemes such as are now forced upon them by persons who have no proper understanding of the actual work. The syllabus is always a compromise and representative of mediocrity ; it never reaches the high-water mark of experience in a subject.

It will be noted that the time prescribed for laboratory work in both years is only twice that to be devoted to lectures. Whether the time be sufficient or not need not be considered ; it is certain, however, that long courses of lectures are now thoroughly discredited as a means of giving elementary instruction.

Turning now to the consideration of the future, the task before us is clearly that of rendering our Universities efficient as educational machines; at present, they are almost beneath contempt as such, owing to the lack of effective organisation—to the lack of true ideals and of active co-operation among their workers; so much is this the case that they may be said to exemplify human frailty rather than human faculty. Taking London as an example, the whole of the University organisation proper is practically worthless, except as a means of retarding progress: the only useful parts are the individual Schools; instead, however, of recognising the importance of these and facilitating, improving and harmonising their work, the University machinery is made use of mainly as a means of stultifying their efforts—the attempt being made persistently to reduce all to one dead level of uniformity.

Dr. Wade is one of those who at the last senatorial election took a prominent part in depreciating the efforts that are being made to develop systems of training suitable to the times by allowing himself to become an advocate of the policy of the Graduates Association. The professed object of this Association is to maintain a rigid, uniform system of examinations for so-called external and internal students alike; and its professed policy is one of antagonism to the teachers in the schools. Of course, the contention is that the agitation is on behalf of the maintenance of a pristine standard, which is painted as having been a very high one—but those who defend this position forget to inquire whether the standard may not have been merely one of difficulty rather than one of excellence; they at least quietly, if not advisedly, ignore this possibility. Those who are behind the scenes know full well that excellence is not thought of. The struggle is between two systems: the one being that of the Schools—in which the attempt is being made to develop practical methods of teaching, having practical ends in view; the other being that of the Coaches—whose object is to secure the immediate success of their pupils at the examinations. The issue will be determined by public decision in favour of one system or the other: the public must determine whether its interests are best served by a system which, if properly administered, cannot but afford training likely to promote efficiency; or by one which tends rather to the stultification of faculty, its end being the immediate, always more or less faulty

solution of a series of Chinese puzzles having no relation to the requirements of life, not competency and skill in doing actual work.

The University machine must be made sound in its working parts, if it is to run smoothly and effectively.

> "What's the good of Mercator's North Poles and Equators,
> Tropics, Zones and Meridian Lines?"
> So the Bellman would cry; and the crew would reply,
> "They are merely conventional signs!"

And so it is with the Senates, Faculties, Boards of Studies and all other such institutions—for the most part, they are mere time-wasting contrivances; the Schools are the one essential feature of the University organisation: if they are guided by true ideals and in honest hands, they may be counted on to do effective work—not otherwise: no mere ordinances can help them; suspicion of the teachers can only nullify their efforts.

To put the teaching of the preliminary medical subjects on a sound basis in London, the first thing to do is to establish a limited number of special Schools. Whatever the present feeling of the various Institutions may be, however jealous they may be of one another, this step will necessarily be taken at no distant date. The public will demand it, as the only means of securing efficient teaching. The development of a suitable course of preliminary studies must be a matter of experiment—it must therefore be in the hands of an independent body of competent teachers: of a School free from interference and independent of external control. If University privileges are to be attached to the Schools, they must be of a certain importance. I imagine that at most three such Schools are required and can be allowed in London. It is most unfortunate that a beginning was not made at South Kensington.

My own personal experience—far from being of the antediluvian order painted by Dr. Wade—enables me to speak with some slight feeling on a proposition such as I advance above. When Prof. Ayrton and I were appointed in 1879 by the City and Guilds of London Institute for the Advancement of Technical Education to start classes in temporary quarters at the Cowper Street Schools, Finsbury, I found plans already drawn for the erection of a separate chemical laboratory on an adjoining site. I at once urged that these should be set aside

and that a more comprehensive scheme should be developed, in order that students might receive the general training required to fit them for industrial posts. Plans were elaborated by us with the assistance of Mr. E. C. Robins, an architect and a member of the governing body; later on, in conjunction with Prof. Perry and Mr. Magnus (now Sir Philip Magnus), we drew up the scheme under which the Finsbury Technical College has been worked practically up to the present day. The passing of a simple examination was made a condition of entrance, from the beginning.

We made it a fundamental condition that there should be no external control through examinations, feeling as we did that it would be impossible to develop suitable courses of instruction if the College were hampered by the necessity of following instructions laid down without any reference to the particular work to be accomplished. The Finsbury College has been a remarkable success; the elimination of external examinations has in no way had the detrimental effect pictured by Dr. Wade (p. 639)—on the contrary. Unfortunately, all the Polytechnics which came into existence subsequently elected to worship at the examination shrine—in most cases their progress has been most seriously hampered by this circumstance. At the close of the Inaugural Lecture which Prof. Ayrton delivered at Finsbury, on November 1, 1879, after referring to the wonderful development of the Japanese during the previous ten years, he pointed out that what the City Companies proposed to do was to give workmen that education which will enable them to commence doing what George Stephenson, half a century ago, urged on them: "Learn for yourselves, think for yourselves, make yourselves masters of principles, persevere, be industrious and then there will be no fear for you."

The keynote of the work at Finsbury was struck in this passage.

When in 1885 we passed to what is now the Central Technical College, together with our colleagues we elaborated a scheme which was dominated by this same policy—again we were uncontrolled by external examinations. The success which has attended the College—the fact that it now ranks as the premier Engineering College in the country—is proof that such a system works well in practice. In point of fact, it would not have been possible, we believe, to achieve success under any

other less elastic system—the constant modification and improvement of the courses which time has shown to be possible and desirable could not otherwise have been effected. The purpose with which students work would have been altogether different: instead of concentrating their attention on their work and acting under the advice of their teachers, they would have constantly had in mind the possible requirements of the examiners and the nature of the Chinese puzzles they would be called upon to answer. Only those who have worked untrammelled by the cast-iron conditions of a rigid system of external examinations are aware of the terrible limitations which such a system imposes upon both teacher and taught.

In both schools, class examinations have always been held. Of late years, we have had the opportunity at Kensington of testing the effect of holding the examinations at the conclusion of the first year's course in conjunction with external examiners appointed by the University of London and of counting the examinations as the Intermediate examinations for the University degree. The examinations, however, have been strictly on the courses and the practical work done during the whole period of study has been taken into account, students being required to have done this as well as the written work satisfactorily. The effect has been altogether good—whereas formerly students would pay little attention to a subject which did not happen to appear in the University syllabus and were liable to neglect their work while preparing to solve examiners' riddles, they now realise that it pays to give serious attention both to lectures and to laboratory work.

The teaching staff at the Royal College of Science, the Royal School of Mines and the Central Technical College have considered the matter together and are unanimous in thinking that the method now applied to the Intermediate is the only proper method to be applied in future to the degree examination (the B.Sc.).

The report has been most sedulously propagated, for political purposes, by Dr. Wade's friends in Convocation that internal students pass the examinations without any effort, far more easily than the external. I know the very reverse to be the case. It is now possible to insist on a high standard of practical work; and it is possible also to penalise the abominable practice of "cooking" results, which seems to be regarded

with entire equanimity by most schoolboys. Under the present external system—although only a few fail to pass who are thoroughly well trained and deserve to succeed, through bad luck in meeting with unfamiliar questions or nervousness—many get through who have no right to pass, being merely crammed for the occasion.

The introduction of the internal system is, in my opinion, the one step of importance taken since the reconstitution of the University—and it was forced on the University by the Schools.

In the course of a speech which he delivered last year, as Chairman, at a dinner of the Graduates Association—which has been printed and widely circulated—the present Vice-Chancellor of the University said that the Association "agreed with Lord Derby in distrusting the teacher as the examiner for degree examinations and does not approve the adoption of degree examinations to fit the teaching of a particular college or Professor." Such a libellous aspersion of the teacher can only be met with the contempt it deserves—but the statement embodies popular doctrine and until teachers are held to be above such suspicion there can be little improvement of their position. The members of the Association who are teachers might well consider whether in thus casting doubt on the honesty of their class, the Chairman is rendering them a service—whether after all they are not catspaws in an agitation which has but commercial ends in view. The narrowness of liberal opinion is too well known to require elucidation and the general tendency to jump at conclusions is well known: but before giving vent to such utterance, the Vice-Chancellor might well have paused to consider whether he and his friends, Lord Derby included, have been in the possession of the knowledge necessary to the formation of a valid opinion. Dr. Wade has described the teaching of my early days as "absolutely destructive of the scientific spirit"—as I had the privilege of numbering the Vice-Chancellor among my pupils, it may be that I am in part responsible for his lack of scientific acumen. But I cannot help thinking that the experience he has had since coming into office and the more intimate knowledge he has gained of the University under somewhat modernised conditions—far removed though these

may be from what is desirable—will have convinced him that his dictum is now not of general application, even if he be not yet prepared to admit that it does not apply at all to true University teaching.

In the case of special schools such as I advocate, the teaching should be entirely under the control of the School, including the examinations on the course held in conjunction with qualified external examiners appointed by the University—whose part, however, should be that of sympathetic advisers rather than that of fault-finding critics. The condition of entry should also be determined by the School alone. It is to be hoped that, at no distant date, examinations such as the London Matriculation will come to an end, as being wholly bad in their influence on the schools from which candidates are drawn: owing to the failure of the University to lay down proper conditions and the lack of competent examiners, there is no real standard of excellence but only one of difficulty.

The matriculation examination may be considered to be of value from two points of view—either as affording proof that the person who passes has received a sound education at school; or as proof of fitness to enter on a course of University study. As at present conducted, it subserves neither purpose properly. It is well known that the requirements are not such as can be directly met by schools and that it is necessary to prepare candidates specially for the ordeal, a thoroughly demoralising proceeding. Moreover, those who have passed the examination, judging from my own experience, are in no way specially fitted to proceed to higher studies. During several years past I have each year had the opportunity of comparing the work done by a considerable number of students who have passed the London Matriculation with that done by at least an equal number who have not submitted themselves to this ordeal: although a distinct difference has been noticeable between the two classes—inasmuch as the former have been more assiduous workers, less anxious to waste their time, being drilled in learning lessons—the one class has not been in any way better prepared than the other to enter upon technical studies. The work done in preparation for the University examination has been in no way of special advantage to the students and has not had the effect of rendering them more intelligent: both classes have been

equally incapable of using their own language effectively in writing accounts of their work, equally untrained in the use of books, equally lacking in manipulative skill. Indeed, the non-matriculated students, on the whole, have had freer minds and from this point of view have been better students. The impression I have gained is that the matriculation is of value only as a proof of ability to pass an examination of a particular type—of the literary type; in fact, the chief tendency of the examination appears to be to bring about the selection of a bookish type of student. I am persuaded that for all practical purposes a properly conducted College entrance examination is both far superior to the matriculation and free from its unfairness—for many are denied access to the University degrees by failure at matriculation who are quite able to follow University courses of instruction with profit, improving vastly as they gain in experience. It is perfectly easy, in a college entrance examination, to judge which of the candidates are likely to be able to follow the courses; in the few uncertain cases, no doubt remains at the end of the first or second term of instruction and incapables are then easily weeded out.

But the whole subject is full of difficulty. At present we are but moving in a vicious circle. The work done in the schools is unsatisfactory as a preparation, in laying a suitable foundation, for the work to be done at the University; the Universities, however, exercise no proper influence on the schools, owing to the academic unpractical character of their entrance examinations. The two centres of activity need to be co-ordinated and to be brought into effective co-operation. The only way in which it appears probable that we may succeed in introducing the desired reforms is by linking up the secondary schools directly with the University schools, by leaving these latter to determine the conditions under which entry to their courses shall be accorded to scholars from secondary schools. But it will be desirable, as far as possible, to dispense with entrance examinations and to exact evidence of training instead. The system in vogue in the Universities of the Middle-West in the United States of America appears to be the one most deserving of trial. This involves the inspection of the secondary schools by *competent* persons from the University schools and the admission forthwith at the University

of pupils from schools duly accredited as providing satisfactory instruction. If during a series of years the pupils from a particular school prove to be unsatisfactory students, the school is struck off the list. A system of this kind would make it possible to bring about the necessary changes in our school system within a very few years—if they entered into the work in the right spirit, University teachers would be able to give advice and assistance to the teachers in the schools which would make it easy for them to improve their teaching. A new spirit of co-operation would be introduced which could not fail to have far-reaching consequences. No headquarters machinery will effect the object I have in view.

Dr. Wade has spoken of the time devoted to preliminary medical studies, especially chemistry—he says, the work cannot be done in less time than is devoted to it at present and more it is impossible to give. The question is one for the future to decide. In my opinion—and I speak from considerable experience—it is undesirable to keep boys and girls at school much beyond sixteen years of age, certainly not beyond seventeen; after this age, they lapse into unsystematic if not irregular habits and are subjected to a discipline unsuited to their years. All further education should be carried on at a place of higher education, under more elastic conditions than school affords and more in sight of the world; under conditions likely to develop independence of character and individuality. On the other hand, it is undesirable, as a rule, that a student should take up serious clinical work under hospital conditions before he is one- or two-and-twenty years of age—the strain is too severe for younger men and the necessary maturity of judgment is rarely developed at an earlier age. From sixteen or seventeen at latest to one- or two-and-twenty should be a period of sufficient length, under proper conditions, for the mastery of the various subjects comprised in the curriculum, short of the purely technical stage. More time could well be found for chemistry than is now given to the subject and as the medical man is, in large measure, a practising chemist, it will come to be recognised, I believe, that he must acquire a sound working knowledge of the subject. Let me add that I would make literary training an important element in the curriculum

As to the teachers—Dr. Wade contends that chemistry must be in the hands of chemists. I agree. But the chemists must be physiologists. The chemistry to be taught will not be mere dry-bones chemistry—anatomical chemistry—but functional chemistry, physiological chemistry in the true sense of the term. Few among our present race of chemists are physiologists even in their own domain; they are mostly mere anatomists. It will be necessary to educate a new type of teacher for the purposes of the medical schools—one who is in full sympathy with medical aims, able to appreciate the character of the problems with which he is faced—a physiological chemist, in fact; it will be necessary, on the other hand, to have physiology taught by chemical physiologists, men who have the same appreciation of chemistry that chemists will have of physiology. The one will have a mastery of the technique of chemistry, the other of the technique of physiology—both sympathising with each other's aims and objects more than either does at present.

As to the state of knowledge of students entering the medical schools, I am quite at one with Dr. Wade that for some time to come it will be necessary to deal with the scientific subjects almost *ab initio*. But I am not inclined to adopt his *laissez-faire* policy as the policy of the future. I hold that it is the duty of the Universities to take the schools in hand without delay and force a sound policy on them. Of what use are Universities if they cannot control the course of higher education—if they do not act as advisers of the public—if they do not promote the spread of new knowledge? The medical schools are now practically all under the control of the Universities. Nothing would be easier than for the Universities to say that after a certain date no one should enter a medical school who could not give evidence of having received sound training previously, during at least three years, in English and the elements of scientific method as applied both to the physical sciences and to biology. Assume that at first many were rejected—parents would be so angry that they would bring pressure to bear on the schools to reform their ways. Some action is needed at the moment which will bring the schools into line with the times—we may be sure that the majority will not change their ways except under compulsion.

If the student be ignorant of scientific method on leaving school, he has not merely wasted precious years: what is far worse is that he has not been disciplined as an observer and experimentalist, as a logical thinker and worker; his mental faculties will have been stunted rather than developed. Unless the art and habit of inquiry be developed in the youthful mind from the earliest days onwards, atrophy of the faculties inevitably sets in, a state of mental inertia being engendered from which it is very difficult to escape. The present system both at school and college is one from which the student receives the minimum of benefit—for the most part the training is not such as to develop scientific habits of mind.

We can apply our knowledge to secure the improvement of appliances—hence the marvellous advance of our civilisation during the past few decades; we can apply it to the study of agricultural problems—to the improvement of plants and brute animals; seemingly, however, we cannot apply it to ourselves. The reason is plain. As Mr. Francis Galton tells us in his *Inquiries into Human Faculty*:

> The vast majority of persons of our race have a natural tendency to shrink from the responsibility of thinking and standing alone; they exalt the *vox populi*, even when they know it to be the utterance of a mob of nobodies, into the *vox Dei* and they are willing slaves to tradition, authority and custom. The intellectual deficiencies corresponding to these moral flaws are shown by the rareness of free and original thought as compared with the frequency and readiness with which men accept the opinions of those in authority as binding on their judgment. I shall endeavour to prove that the slavish aptitudes in man are a direct consequence of his gregarious nature, which itself is a result of the conditions both of his primeval barbarism and of the forms of his subsequent civilisation. My argument will be, that gregarious brute animals possess a want of self-reliance in a marked degree; that the conditions of the lives of these animals have made a want of self-reliance a necessity to them and that by the law of natural selection the gregarious instincts and their accompanying slavish aptitudes have gradually become evolved. Then I shall argue that our remote ancestors have lived under parallel conditions and that other causes peculiar to human society have acted up to the present day in the same direction and that we have inherited the gregarious instincts and slavish aptitudes which have been needed under past circumstances, although in our advancing civilisation they are becoming of more harm than good to our race.

If science is to be of any value to us, it should enable us to bring influences to bear to counteract the innate peculiarities which tend to diminish human efficiency. At present, education,

as a rule, has an effect opposite to that which we desire to produce.

My proposals, it will be obvious, are far reaching. They involve, in London, the reorganisation of the University and the recognition of its Schools as dominant factors. All who are in the inner circle and who understand the working of the machine —or rather its failure to work—are aware that it comprises incompatible elements and interests: the recognised Schools, the evening schools or Polytechnics, the coaches and their following —the so-called external students. Our plain duty now is to reconstitute it as an effective organisation in which teaching can take place under conditions of maximum efficiency.

The situation is clearly foreshadowed in the following luminous lines:

"'Tis a pitiful tale," said the Bellman, whose face
Had grown longer at every word:
"But, now that you've stated the whole of your case,
More debate would be simply absurd.

"The rest of my speech" (he explained to his men)
"You shall hear when I've leisure to speak it.
But the Snark is at hand, let me tell you again!
'Tis your glorious duty to seek it!

"To seek it with thimbles, to seek it with care;
To pursue it with forks and hope;
To threaten its life with a railway share;
To charm it with smiles and soap!

"*For the Snark's a peculiar creature, that won't*
Be caught in a commonplace way.
Do all that you know and try all that you don't.
Not a chance must be wasted to-day!

"For England expects—I forbear to proceed:
'Tis a maxim tremendous but trite:
And you'd best be unpacking the things that you need
To rig yourselves out for the fight."

THE BIO-CHEMISTRY OF ANIMALS AND PLANTS

A COMPARATIVE STUDY.—I

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Chemistry, at one time intimately connected with biology, drifted away from this science during the past century, mainly owing to the apparent exhaustion of its methods in their useful application to biological problems. Meanwhile the edifice of chemistry has been perfected to such a degree that chemists are again able to attack biological questions with the help of new experimental methods. In consequence it is being more and more recognised that the sharp separation of animal and vegetable biology has only been an artificial one and does not really exist. Formerly it was held that the plant alone possessed the power of building up organic substances, *i.e.* of synthesis. The animal body, it was thought, had mainly the function of breaking down the substances supplied to it by the plant. The first synthesis taking place in the animal body was demonstrated by the classical work of Wöhler in 1824, when he showed that benzoic acid in its passage through the body was linked up to glycine and excreted as hippuric acid. Many similar instances of synthetical processes occurring in the animal body have since been found (to mention only the latest one, *i.e.* the synthesis of proteins from amino acids), and although no doubt the synthetical power of the animal organism is less than that of the plant, we know now many biological processes which are common to both.

The purpose of the following pages is to discuss in outline some of the progress made in this "Grenzgebiet" (borderland) of bio-chemistry.

The Nitrogenous Cycle

If we consider first the nitrogenous substances which play such an important rôle in the animal organism, it is evident that

they occur there in far larger proportion than in the plant, whereas the latter contains a preponderance of carbohydrates and other substances which are free from nitrogen. Here we are at the outset confronted with a fundamental difference between animals and plants, which seems to find an explanation, if we consider that the nitrogen supply of plants (apart from atmospheric nitrogen) is not at all abundant, whilst on the other hand in the carbonic acid of the air, which by the aid of the energy of sunlight they are able to transform into carbohydrates, plants possess a seemingly inexhaustible supply of carbon. Nitrogen-free carbon compounds accordingly perform functions in the plants for which there is no analogy in the animal organism, *e.g.* cellulose, in the cell membrane. It can, however, be easily demonstrated that a sufficient supply of nitrogen is one of the essential factors for plant life, and that the protoplasm of the plant contains proteins as certainly as does the protoplasm of an animal; further, that the properties and behaviour of the vegetable proteins are very nearly allied to those of animal origin.

It is a fascinating problem, which the comparative study of vegetable and animal biology has helped to solve, to investigate the great cycle of nitrogen in Nature. Here again we meet with another fundamentally important difference of animal and vegetable metabolism. The animal organism relies as the only source for its protein anabolism either on protein itself or on its direct cleavage products. It is unable to form protein material from inorganic compounds, nor does the animal cell possess the property of utilising other organic nitrogenous compounds, which have no direct relation to proteins. The animal organism, in short, depends entirely for its source of nitrogen on the vegetable world.

The raw products available to the plant for the synthesis of proteins are, mainly, the free nitrogen of the atmosphere, ammonia salts, nitrates and nitrites in the soil and organic nitrogenous substances of various kinds which are furnished by the decomposition and decay of animals and plants, such as amides, amines, amino acids, and amino salts of organic acids.

In the protein synthesis of the plant from these materials a most important rôle is played by bacteria, those micro-organisms which take an intermediate place between animals

and plants. The recognition of their importance is entirely the outcome of modern methods of investigation. This knowledge is of recent origin, and a short consideration of the main changes produced in nature by bacterial activity is essential in order to understand the nitrogenous cycle.

Nitrification.—As a final product of decay of plants or animals brought about by micro-organisms, the nitrogenous substances furnish mainly ammonia. This is transformed in the soil into nitric acid and nitrates, and enormous deposits of saltpetre have been formed in this way on the earth's surface under certain conditions. It was originally pointed out by Sir Humphry Davy that saltpetre is formed by the help of the oxygen of the air from the ammonia present in the soil, but the fact that this saltpetre formation, now usually called nitrification, is due to a biological process, carried out by the activity of microbes, has only been demonstrated in recent times. It was not until 1890 that Winogradsky succeeded in producing pure cultures of these organisms. This achievement offered great difficulties until it was found that these organisms grow best in a completely inorganic medium. They are able to obtain all their necessary carbon and nitrogen from ammonium carbonate. This nitrification process is the work of several kinds of microbes, one class called "nitrosomonas," oxidising ammonia to nitrites, and the other class, called "nitrobacter," which oxidise nitrites to nitrates. It has been shown that a large amount of organic nitrogen is transformed into nitrates in the soil and thus it is made available for the building up of the protein material of vegetable protoplasm. This is used as food for animals, and the largest amount of the protein-nitrogen of food is excreted by them in the urine, as urea or uric acid, to be transformed, also by bacterial activity, into ammonia and finally in the soil into nitrates.

Denitrification.—Whilst the nitrogenous cycle would thus appear to be a relatively simple one, another very old observation seems to break its continuity. Long ago Davy discovered that free nitrogen is formed in large quantities during the decomposition of organic substances. Towards the end of last century it was finally established that we have to deal here also with the work of microbes, which, however, work only in the absence of oxygen. This process is called "denitrification," and the organisms which are the

cause of it reduce nitrates to nitrites and ammonia, and finally to free nitrogen. So active are some of them in pure cultures that the process of nitrogen evolution resembles an alcoholic fermentation and has been aptly termed "nitrate fermentation." There cannot be the slightest doubt that by this process there is continually set free on the surface of the earth an enormous quantity of nitrogen which is apparently lost to organic life.

N-Fixation. — A solution of this apparent contradiction, although already foreseen by Berthelot, has finally been furnished and proved by the exact experimental work of Winogradsky. He succeeded in 1893 in isolating a bacillus, called by him *Clostridium Pasteurianum*, from the soil which is able to utilise directly the nitrogen of the air for building up its protein substance. A large number of similar microbes, mainly anærobes, have subsequently been isolated by other workers. That the absorption of nitrogen by these organisms takes place in large quantities is proved by experiments on trial fields, and it has been calculated that about 30 kg. nitrogen per acre are made available yearly.

This is, however, not the only way by which the atmospheric nitrogen is utilised by organic life.[1] It has long been accepted amongst farmers as a well-established fact that wheat grows better on fields on which previously leguminous plants such as clover had been grown. Biologists took no notice of this result of practical experience until quite recently. The whole process has now been completely cleared up, the work beginning with the careful investigations of Hellriegel in 1886. He was the first to establish accurately the fact that leguminous plants possess the property of absorbing atmospheric nitrogen, and he showed the connection of this property with the formation of root nodules and the presence of bacteria. To Beijerinck (1886) belongs the merit of having succeeded in isolating these bacteria in pure cultures and showing that a bacillus, called by him *B. radicicola*, enables the plant by a symbiotic process to absorb elementary nitrogen from the atmosphere and to make use of it for its growth. These

[1] An allusion might here be made to the successful modern methods of nitrogen fixation from the air by electro-chemical means (calcium-cyan-amide, calcium nitrate). As it has been stated that the saltpetre fields of Chili will be exhausted within the next fifty years, such considerations are of practical importance.

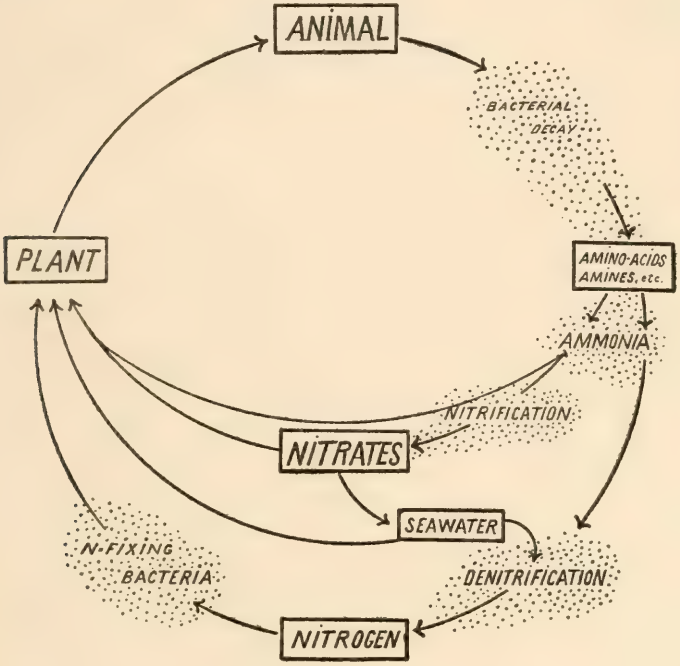
observations have been extended by Nobbe, Hiltner, Frank, Moore, and others[1] and showed that many strains of this bacillus exist and that a favourable influence on artificial infection is only noticed when cultures obtained from nearly related families are used, *e.g.* bacteria from peas will produce nodule formation in peas, but not in robinia roots. It is also interesting to note that the Japanese *Soja hispida* very often does not grow nodules in European soil, but produces them when inoculated with Japanese soil. Nothing is known so far about the initial products formed by the bacteria from nitrogen, but it is assumed that proteins are finally produced which are made use of by the plant.

Still another stage in the nitrogen cycle must be mentioned, since it helps us to understand the conditions of plant and animal life in sea-water. By the solvent agency of rain-water, soluble nitrogenous substances such as nitrates are drained out of the soil and finally carried by rivers into the sea. An enormous amount of nitrogen (Brandt calculates it at 40,000,000 gr. per annum) is thus lost to the dry land, and this is largely in excess of that nitrogen removed from the sea in the same period in the form of food fishes and other animals. The question arises, how these large quantities of nitrogen are again returned to circulation, and in this direction the discovery made by Baur in 1902 is of the greatest importance. He demonstrated the general occurrence of denitrifying bacteria in sea-water and mud. These continually throw again into circulation the nitrogen carried into the sea by the rivers, or which has accumulated there owing to the decay of plant or fish life. The discovery of the denitrifying bacteria in sea-water also helps us to solve another apparent contradiction. On the dry land the tropical and subtropical regions are more thickly populated by plant and animal life than the regions nearer the poles, whereas in the sea just the reverse is the case. In accordance with this the nitrogen content of southern warmer sea areas is smaller than that of northern colder ones. Now it has been shown that the development of the denitrifying bacteria stands in close relationship to temperature. Whilst at the temperature of the tropical seas (25–30°) the nitrogen evolution is most marked, the denitrifying bacteria are con-

[1] For a complete list of the literature from Pliny to 1901, see E. Jacobitz, *Centralb. f. Bact.* II. vol. vii. 1901, 783.

demned to inactivity at the low temperatures of 4–15° of the northern seas, and thus the nitrogenous materials are left available for plant and subsequently for fish life.[1]

We are now able to finish the picture of the nitrogen cycle in Nature, and the following schematic drawing is left to speak for itself:



THE SYNTHESIS OF PROTEIN IN PLANTS

Moulds.—The statements that some fungi (*Aspergillus* and *Penicillium* varieties) are able to fix atmospheric nitrogen like certain bacteria have so far not been sufficiently established. Moulds and yeasts, however, are able to satisfy their nitrogen want by making use of ammonia salts and nitrates. For yeasts, nitrates are less suitable than for moulds. It has further been shown that the latter synthesise their protein material still better if simple amino acids are offered to them. For one of the commonest moulds, *Aspergillus*, it was demonstrated by

[1] For a detailed account of these and similar problems, see J. Johnstone, SCIENCE PROGRESS, vol. ii. 1907, 191.

Czapek and by Emmerling that the food value of the *a*-amino acids is superior to that of all other nitrogenous substances. Abderhalden and Rona proved subsequently that this mould builds up its protein in the same way, if grown on potassium nitrate, glycine, or glutaminic acid, and that the protein thus formed in the living organism remains constant in composition, *i.e.* furnishes identical cleavage products on hydrolysis. As an explanation for this interesting observation we must assume that the *Aspergillus* starts with the amino group in the building up of its protein.

Yeasts.—A subject of considerable biological interest and at the same time of practical value is the study of the nitrogenous metabolism of yeast. To mention the name of "fusel oil" in this connection seems to be going away from the subject, but it is not really so, for the intimate association of protein formation and "fusel oil" has been made clear by the researches of F. Ehrlich, and these deserve to be referred to in some detail.

Of the various by-products of the alcoholic fermentation of carbohydrates by yeast (such as glycerin, succinic acid, ethers, aldehydes, etc.), fusel oil is the least desirable from the distiller's point of view. It was discovered by Scheele in 1785, and was shown by Pasteur to consist of higher alcohols and especially two amylic alcohols. Its smell and taste are disagreeable, and the deleterious action of certain raw spirits has, although probably without justification, been ascribed to it. The separation of fusel oil from ordinary ethyl alcohol was one of the difficulties of alcohol manufacture, which was finally solved by the perfection of fractional distillation. With the introduction of better methods, especially the use of pure yeast cultures, a distinct falling off in the quantity of fusel oil formed took place, whilst on the other hand the demand for this product for industrial processes rose to such an extent as to produce a scarcity in the world's markets. Amylic alcohol in the form of its ethers is now in great demand for the manufacture of fruit essences, celluloid, and smokeless powders. While investigating the conditions of fusel-oil formation, the view found most general acceptance that its origin was due to a bacterial decomposition of sugar. The fact, however, that the alcohols of fusel oil possess a branched carbon-chain, and that the addition of the

so-called "fusel bacteria" did not increase the output of fusel oil in normal fermentation, soon disposed of this idea.

To F. Ehrlich belongs the credit of having discovered the exact conditions for the production of fusel oil, and its close connection with protein synthesis from amino acids in the growing yeast cell. The application of the results of modern researches on protein constitution, and the amino acids produced by its cleavage, led him to this solution. He discovered iso-leucine in molasses as well as in yeast, and as a constant proteolytic cleavage product of other proteins (fibrin, caseinogen), and this, together with the general occurrence of amino acids in plant juices and the similarity in constitution of leucine to iso-amylic alcohol, led him to the view that amylic alcohol and its homologues are produced from amino acids by the agency of yeast itself. The conclusive proof for the correctness of this view was the discovery that the fermentation of these amino acids by means of pure yeast cultures occurs in the presence of sugar. In this way Ehrlich succeeded in obtaining iso-butyl alcohol from valine, iso-amylic alcohol from leucine, and d-amylic alcohol, the only optically active constituent of fusel oil, from iso-leucine in quantities corresponding to the amount of amino acid which he had added. Whilst the highest percentage of fusel oil of raw spirit was formerly 0·5 per cent., it is now possible by these means to increase it ten to twelve times.

The formation of the higher alcohols from the amino acids admits of a very simple chemical explanation. With the addition of water a simultaneous splitting off of CO_2 and NH_3 takes place, as expressed by the following formulæ[1]:

leucine.

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH\,.\,CH_2\,\underset{*}{C}H\,.\,(NH_2)\,.\,COOH + H_2O =$$

iso-amylic alcohol.

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH\,.\,CH_2\,.\,CH_2OH + NH_3 + CO_2$$

iso-leucine.

$$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>\!\underset{*}{C}H\,.\,\underset{*}{C}H(NH_2)\,.\,COOH + H_2O$$

d-amylic alcohol.

$$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>\!\underset{*}{C}H\,.\,CH_2\,.\,OH + NH_3 + CO_2$$

During the growth of the yeast cell these reactions probably

[1] $\underset{*}{C}$ = asymmetrical carbon atom.

take place by means of an enzymatic action, and the ammonia is directly used up for the formation of protein. The fusel-oil formation depends not only on the amount of amino acids, but also on the kind and quantity of other nitrogenous substances present. In the presence of easily assimilated nitrogen, such as asparagine or ammonium salts, practically no fusel oil is formed. Ehrlich has also applied this process for the preparation of optically active amino acids from the racemic inactive compounds, one component only being transformed into the corresponding alcohol. But not only is yeast able to use leucine and iso-leucine as a source of nitrogen for its protein formation, but also all the other *a*-amino acids, *e.g.* tyrosine is converted into p-oxy-phenyl-ethyl alcohol, and phenyl-alanine furnishes phenyl-ethyl alcohol. The formation of this latter substance, which represents the largest bulk of the essential oil of roses, opens a new outlook for another branch of plant physiology, the formation of essential oils and their connection with proteins.

Carnivorous Plants.—Of great interest is the existence of plants which secrete products analogous to the digestive juices of animals, and which are able to digest insects or proteins. This great group of carnivorous plants comprises *Drosera*, *Pinguicula*, and *Utricula* varieties, etc. The various kinds of *Nepenthes* act on a larger scale, catching and digesting insects by means of the liquid in their pitchers. It is still doubtful whether the action of these enzymes corresponds to that of pepsin or trypsin, although some recent preliminary experiments by Abderhalden and Terunchi make it probable that it is not of a trypsin nature. They found that the dipeptide glycyl-l-tyrosine is a very convenient substance to distinguish between pepsin and trypsin, as it is not attacked by the former, but easily split into its components by the latter. The juice of *Nepenthes* has no appreciable action on this dipeptide. Recently Vines has succeeded in showing that an enzyme of the nature of erepsin occurs largely in plants and also to some extent in *Nepenthes* pitchers. This enzyme was originally discovered by Cohnheim in the intestinal mucous membrane, and it was shown by Vernon to be generally present in all animal tissues. It has no action on proteins as such, but splits peptones, albumoses, and polypeptides into amino acids. One would expect that the carnivorous plants would be able to

use amino acids themselves or higher cleavage products for their protein synthesis. There has been very little work done on the metabolism of carnivorous plants, and this point has not been investigated. That plant organisms exist which produce their protein from the higher cleavage products alone has, however, been made clear by the researches of Beijerinck, who proved that the alga living symbiotically with *Physcia parietina* requires peptones (*i.e.* albumoses) for its normal growth.

Higher Plants.—Relatively little is yet known about the protein synthesis in plants containing chlorophyll. The study of the processes occurring during germination has attracted many investigators, and has furnished most useful results. The ripe seeds nearly always contain a large store of protein. As soon as germination begins great changes take place in cells. The proteins are decomposed by the action of proteolytic ferments, the existence of which, during germination, has been definitely proved. By the action of these ferments the higher cleavage products first obtained from the proteins are finally converted into simple amino acids, which are partly at least made use of at once by the growing plant. We may compare the process of germination with that occurring during digestion in the animal body. In both cases the complex food protein is first decomposed into simpler cleavage products, and it is from these that the organism reconstructs the protein matter of its protoplasm. A long series of amino acids, leucine, tyrosine, aspartic acid, glutaminic acid, arginine, lysine, histidine, etc., have been isolated from germinating seeds. A peculiar occurrence is the formation of asparagine and sometimes of glutamine, substances which have not been observed in any artificial protein hydrolysis. By allowing seeds to germinate in the dark, *i.e.* under normal conditions, large amounts of these two substances may be produced. The significance of asparagine formation is not yet fully understood. Pfeffer has shown that the increase of the asparagine is coincident with the decrease of carbohydrate formation in the absence of light, which stands in close relationship to the protein synthesis, the absence of which entails an accumulation of amino acids. It is possible that asparagine represents a transition stage in the formation of other nitrogenous substances, or perhaps that it is connected with carbohydrate and fat formation. This view is confirmed by certain observations made upon tyrosine. This amino acid

is produced in large amounts during the initial stages of the germination. By the action of a ferment, which can easily be localised, it is, however, very quickly converted into a nitrogen-free substance—homogentisinic acid. This same substance, by the way, is formed from tyrosine in the human body under certain abnormal conditions and excreted in the urine, giving rise to so-called alkaptonuria.

After the exhaustion of the nitrogen supply from the seed, the plant depends for its nitrogenous foods on the nitrates and ammonia salts of the soil. Those plant organs seem to be predestined to carry out the protein synthesis in the adult plant, in which carbohydrate formation is also most vigorous; and it was pointed out by Sachs in 1865 that the leaves perform the largest share of this work. Very little definite knowledge exists with regard to the actual processes. It is generally accepted now that the first substances formed are amino acids, and that by the linking of these together into complex chains the proteins are ultimately produced. Light plays a most important part in the protein formation in leaves. Whilst leaves are unable to make use of free nitrogen, several observations confirm the view that small amounts of ammonia are absorbed. The protein synthesis in leguminous plants, which takes place by the help of bacteria, has already been discussed (p. 679).

Protein Synthesis in the Animal Organism

Since Loewi's experiments, which showed that in animals weight, health, and nitrogenous equilibrium can be maintained for a considerable time by feeding them on the crystalline cleavage products of protein hydrolysis, the old view that the albumoses and peptones are absorbed as such has been steadily losing ground. The belief is now general that the largest part of the ingested protein undergoes cleavage into its fundamental amino acids, and that the body exerts a selective power in building up its various proteins from these comparatively simple materials. Evidence is accumulating which confirms this view, and of the many researches in this direction, those of Abderhalden and his collaborators should be specially mentioned.[1]

[1] This question has been fully discussed by F. G. Hopkins, Science Progress, vol. i. 1906, 159, and by E. P. Cathcart, *ibid.* vol. ii. 1907, 76.

The Vegetable Proteins

The preponderance of carbohydrates in plants explains the fact, shown in the history of plant physiology, that the general occurrence of nitrogen in plants has been recognised relatively late, and that the presence of proteins especially has been considered as an exceptional occurrence.

History.—From an historical point of view it is interesting to note that the earliest known vegetable protein was wheat gluten; this was isolated by Beccari in the eighteenth century. Berzelius examined it at the beginning of last century and called it "vegetable glue" or "vegetable casein" on account of its similarity to the corresponding animal substances. Braconnot isolated about the same time the proteins of peas and beans, which he called "legumin." Gay-Lussac subjected vegetable proteins to elementary analysis, and was the first to point out the general occurrence of proteins in seeds. But Liebig and his pupils were the real founders of the system which led to our modern knowledge of protein chemistry. He distinguished between plant albumin (coagulated by heat, not precipitated by acids), plant casein (not coagulated by heat, not precipitated by acids), and plant fibrin. The view also originated from his laboratory that elementary analyses of proteins teach us very little about the nature of these substances and that more knowledge is obtained by the investigation of their hydrolytic cleavage products. The classical work of Ritthausen, published in 1872, was the outcome of the application of these methods to vegetable proteins. Ritthausen's work still remains of importance, although his methods have been superseded by the introduction of neutral salts for the purpose of isolation and separation of proteins. The names of Hoppe-Seyler, Weyl, Schmiedeberg, must be mentioned in this connection. It was mainly Kühne's pupil, Chittenden, and later Osborne, two American workers who applied the method of fractional salt precipitation to vegetable proteins. This method is still a valuable one, and it is to be hoped that together with the latest processes for the isolation of hydrolytic cleavage products, which we owe to the genius of E. Fischer, we shall be able in the near future to form clearer ideas of the constitution of proteins.

Occurrence and Properties.—With regard to most of the

proteins of leaves and roots we are ignorant of the state in which they are present in the cell sap and the cell protoplasm, and indeed in most cases the proteins of the fully grown plant have received but little attention. The best-known vegetable proteins are those which occur stored up in the seeds as "reserve" food for the growing organism, and they show many analogies with the corresponding animal proteins. As a rule they resemble in their chemical and physical behaviour the animal globulins, *i.e.* they are insoluble in water, but soluble in salt solutions and precipitated by dilution or by removal of the salts by dialysis. They crystallise very often inside the cell itself and they were the first crystallised proteins known (Hartig, 1853). Protein crystals are found especially in the endosperm of oily seeds, in the so-called "aleurone" grains (especially of the Para nut, castor-oil seed, etc.). From their solutions they can again be obtained in a crystalline form by relatively easy means. The methods introduced by Hofmeister for the crystallisation of egg albumin have not yet been applied to vegetable proteins. It is a remarkable fact that whilst the vegetable globulins crystallise most easily, the animal globulins have not yet been obtained in crystalline form.

Most of the vegetable proteins, however, like those of the animal body, are characterised by their colloidal nature. Still, numerous transition stages between the colloid and crystalloid condition are also found; thus many vegetable proteins are soluble in alcohol, have lost their property of being coagulated by heat, and have a diminished viscosity. The vegetable proteins examined so far are all lævo-rotatory.

Constitution of the Protein Molecule. Protein Hydrolysis.— Elementary analysis and the study of the physical properties and chemical reactions of the animal and vegetable proteins have led to their classification into more or less well-defined groups. These are subdivided according to purely external characteristics, such as origin, solubility, coagulability, etc. On the basis of such properties we distinguish to-day some forty to fifty natural proteins, and this number will probably increase as the methods of differentiation are improved. A better knowledge of the probable constitution of the protein has, however, resulted from the attempts to study systematically their cleavage products. The means which were made use of to obtain this end were the action of enzymes, of acids and alkalies in varying

proportions, of water under increased pressure, of oxidising and reducing agents, etc. Of all these methods two have led to the most constant and useful results—namely, hydrolysis by means of ferments and by dilute mineral acids—and these methods play at present a most important rôle in protein chemistry. Whilst the last method has led to a knowledge of the final cleavage products, the intermediate substances, which still show protein characters, have been made available for further study by the use of enzymes. The well-known stages of enzyme action are the albumoses or proteoses, the peptones and amino acids. Only quite recently E. Fischer has demonstrated an intermediate stage between the peptones and the amino acids by the isolation of the so-called polypeptides, which promise to be of the highest importance for the chemistry and biology of the proteins.

The ideal aim of the chemist would be to separate the complex mixture of cleavage products quantitatively in such a way as to account for the whole of the carbon, nitrogen, and sulphur in the original protein. This idea will, however, probably never be attained on account of the secondary reactions taking place during hydrolysis, such as formation of brown and black pigments, splitting off of CO_2, etc. Even with the best methods at his disposal, E. Fischer has succeeded so far only in separating at the utmost 50 to 70 per cent. of the amino acids present in the cleavage products.

Under these circumstances it is of the greatest value to be able to obtain by a short and reliable procedure at least an approximate knowledge of the nitrogen distribution in the protein molecule, even if this does not allow us to determine quantitatively the single cleavage products. Such a method has been worked out, mainly in Hofmeister's laboratory, by Hausmann, and has been subsequently found trustworthy by Osborne and others.

Hausmann's method is shortly as follows: The whole nitrogen of the protein is estimated by Kjeldahl's method. A weighed amount of the substance is then hydrolysed by means of hydrochloric acid. After complete hydrolysis the cleavage products are separated into three classes, and the nitrogen estimated in each by means of Kjeldahl's method as—

1. Amide-N or ammonia nitrogen. This comprises the nitrogen of that part of the protein molecule which is easily

split off as ammonia, and is determined by distilling off the ammonia with magnesia.

2. Diamino-N. The fluid, free from ammonia, is precipitated by phosphotungstic acid, and the nitrogen present in the precipitate determined. This represents the nitrogen of most of the diamino acids, such as histidine and arginine.

3. Monoamino-N is estimated in the residual fluid after removal of the amide and diamino-N.

Although this method is not absolutely correct, it has nevertheless furnished most valuable information when applied to different animal and vegetable proteins, as is shown in the following table from the analyses of Osborne:

	Total N.	Amide-N.	Diamino-N.	Monoamino-N.
Zein (maize)	16·13	2·97	0·49	12·51
Hordein (barley)	17·21	4·01	0·77	12·04
Gliadin (wheat)	17·66	4·20	0·98	12·41
Glutenin (wheat)	17·49	3·30	2·05	11·95
Globulin (wheat)	18·39	1·42	6·83	9·82
Leucosin (wheat)	16·93	1·16	3·50	11·83
Edestin (hemp)	18·64	1·88	5·91	10·78
Excelsin (Para nut)	18·30	1·48	5·76	10·97
Caseinogen (milk)	15·62	1·61	3·49	10·31

These figures show interesting differences between otherwise similar proteins. New characteristics are given for some protein groups, *e.g.* the alcohol soluble vegetable proteins, which possess a high amide-N and low diamino-N. In Osborne's analyses (not given) of various so-called edestins, great differences of the diamino-N was revealed. The method has also proved useful for the differentiation of albumoses (Pick), and interesting deductions as to the food value of various proteins were drawn from its results (Blum). As 80 to 90 per cent. of the carbon of proteins (according to Kossel) is present in combination with nitrogen, the method is likely to give important clues as to the constitution of different proteins.

Cleavage Products.—The following is a list of the main substances so far met with among the hydrolytic products of proteins; they are classified roughly under the divisions of Hausmann's method, and in each case the constitutional name and discoverer of these substances are given:

Monoamino-N

Glycine (amino-acetic acid, Braconnot 1820).
Alanine (amino-propionic acid, Weyl 1888).
Valine (amino-valerianic acid, Gorup-Besanez 1856).
Leucine (amino-caproic acid, Proust 1818).
Iso-leucine (amino-caproic acid, Ehrlich 1903).

Serine (oxy-amino-propionic acid, Cramer 1865).
Phenylalanine (phenyl-amino-propionic acid, Schulze and Barbieri 1881).
Tyrosine (oxy-phenyl-amino-propionic acid, Liebig 1846).
Tryptophane (indole-amino-propionic acid, Hopkins and Cole 1901).

Aspartic acid (amino-succinic acid, Plisson 1827).
Glutaminic acid (amino-glutaric acid, Ritthausen 1866).

Proline (pyrrolidine carboxylic acid, Fischer 1901).
Oxyproline (oxy-pyrrolidine-carboxylic acid, Fischer 1902).

Diamino-N

Ornithine (diamino-valerianic acid, Jaffe 1877).
Lysine (diamino-caproic acid, Drechsel 1889).
Arginine (amino-guanidine-valerianic acid, Schulze and Steiger 1886).
Histidine (amino-imidazole-propionic acid, Kossel 1896).
Diamino-trioxy-dodecanic acid (Fischer and Abderhalden 1904).
Cystine (diamino-dithio-d-lactic acid, Wollaston 1810).

The proportions in which the various amino acids are obtained from different proteins vary considerably. The quantitative examination of various proteins, by the help of the methods introduced by A. Kossel and E. Fischer, is being carried out at present in many laboratories, and has already furnished most valuable results, *e.g.* albumins are distinguished from globulins by their complete lack of the glycine group, whilst on the other hand gelatin furnishes as much as 17 per cent. of this substance. The latter protein, however, does not yield

any tyrosine or tryptophane. The alcohol-soluble vegetable proteins are characterised by their complete lack of glycine and lysine, and are especially rich in glutaminic acid (gliadin of wheat containing 36 per cent.). Some animal proteins, such as the protamines, yield enormously high percentages of arginine (salmine = 84 per cent.). It is worth noting in this connection that in the hydrolysis of all important proteins which play the chief part in animal or vegetable metabolism, all these amino acids occur almost without exception, so that the conclusion must be drawn that none of them can be dispensed with in organic life.

Synthesis.—The study and isolation of the hydrolytic cleavage products have thus been shown to be of the greatest importance. As the same substances are not only formed by the action of acids and alkalies, but also by the agency of the digestive enzymes, they are to be regarded as the true "Bausteine" (building stones), of which the complicated protein molecule is built up. Starting from this idea E. Fischer has been able to build up, by linking together simple amino acids (a process the reverse of hydrolysis), substances which he called polypeptides. These are very similar to the polypeptides which he isolated from digestive mixtures, and even some of the relatively simple ones, such as l-leucyl-triglycyl-l-tyrosine, exhibit many of the properties of the albumoses. The octa-deca-peptide derived from fifteen molecules of glycine and three molecules of leucine, having the high molecular weight of 1213, is a substance which, in its external properties, closely resembles many natural proteins. More than one hundred of these artificial polypeptides have already been synthesised, and we may expect in the near future the announcement of the synthesis of what E. Fischer regards as the simplest protein, namely silk-fibroin, which according to his researches only contains four different amino acids.[1]

Classification of Vegetable Proteins.—The classification of the proteins in general is at present under revision, and can only be a provisional one in view of the rapid progress being made in their chemistry. It is possible that shortly the increased knowledge of the cleavage products and their quantitative

[1] For a complete account of Fischer's work see his book, *Untersuchungen über Aminosäuren, Polypeptide und Proteïne*, 1906; also R. H. Aders Plimmer, SCIENCE PROGRESS, vol. ii. 1907, 88.

relationships will produce an important change in our present classification. With regard to the vegetable proteins, this is all the more desirable, as they can only be fitted in with difficulty into the present system. A complete up-to-date treatise[1] of the vegetable proteins has still to be written, and their nomenclature and classification are at present in a most unsatisfactory and perplexing state. For the purpose of this paper the material to be dealt with has been divided into four main classes, it being recognised, however, that this classification can only be a tentative one, and open to criticism.

The following classes are proposed:

1. Phyto-albumins.
2. Phyto-globulins.
3. Gliadins (alcohol-soluble proteins).
4. Phyto-caseins (phyto-vitellins).[2]

1. The proteins of the first class are the least known of vegetable proteins, the reason for this being that the seeds, which form the main source for the study of plant proteins, contain albumins only in relatively small proportions. Many observations show, however, that they are also present in leaves and the cell-sap of other parts of plants.

The vegetable albumins possess the same characteristics as those of animal origin. They are soluble in water and salted out by ammonium sulphate and other salts. They require a larger amount of salt for their precipitation than the globulins. They may be separated from the latter by dialysis, remaining in solution after the removal of the salts. They have not yet been obtained in a crystalline form, are coagulated by heat, and show all the typical colour reactions of the proteins. They are phosphorus-free.

The best known of the vegetable albumins is a substance called *leucosin*. It occurs in small quantities in grasses, but has been prepared mainly from wheat grains (also rye, barley, and maize), in which seeds it is present to the extent of 0·3—0·4

[1] Only two exhaustive treatises exist on vegetable proteins: *Die Eiweisskörper der Getreidearten*, etc., Ritthausen, 1872; and *Die Proteide der Getreidearten*, etc., Griessmayer, 1887. The latter is a translation of Chittenden and Osborne's collected older papers.

[2] The name "Glutelin" has recently been proposed by a committee of the American Physiological Society for these substances.

per cent. For its preparation the seeds are extracted with water or dilute salt solutions, the whole of the dissolved proteins precipitated by saturation with ammonium sulphate, and a solution of the precipitate subjected in dialysis. The globulins become insoluble with the removal of the salt, and from the remaining aqueous solution leucosin may be precipitated in the usual way. It is coagulated at a temperature of 52°; this is lower than the heat-coagulating point of the corresponding animal albumins. It contains 16 per cent. N. and 1·5 per cent. S. and on hydrolysis it furnishes nearly four times as much mono-amino-N as diamino-N.

2. *The Phyto-globulins.*—The best-known vegetable proteins belong to this class, and they represent the main reserve proteins of the seeds. Their properties are so much like those of the animal proteins that they have been considered by Chittenden and Osborne—to whom we are mainly indebted for our knowledge about them—as directly analogous to the animal globulins. The ease with which many of them assume a crystalline form, however, distinguishes them from the animal globulins. It is true that lately a doubt has been expressed by Wiman as to their globulin character, as he found 0·4 per cent. phosphorus in legumin, the globulin of peas. But Osborne upholds his view that the purified substances must be considered as phosphorus-free real globulins. Only phosphorus-free proteins ought to be included in this class.

The best-known representative of this class, and one which, on account of its easy preparation, has been most thoroughly examined, is *edestin.* It seemed from their properties and composition that the various crystallised globulins called edestin, and obtained from the seeds of wheat, oat, maize, sunflower, cucumber, cotton, flax, and hemp, represent all one and the same substance. But the analysis by Hausmann's method, carried out by Osborne and Harris, revealed distinct differences in their molecular constitution. Edestin is easily prepared in large quantities from hemp-seed, which contains about 6—8 per cent. edestin. The seeds are first treated with benzene, to remove the oil, then extracted with 5 per cent. salt solution at 60° C., and filtered warm. On cooling, edestin crystallises out, and may be easily recrystallised in the same way. It usually forms well-defined octahedra, but on slow crystallisation prismatic crystals may be obtained. Its insolubility in water distinguishes

it from the albumins; it is, however, easily soluble in salt solutions, and gives most of the usual protein tests. It contains 18·5—18·8 per cent. N and 0·8—0·9 per cent. S, and is phosphorus-free. Its heat-coagulation temperature is at about 90°, much higher than that of the animal globulins. Abderhalden has recently examined its cleavage products.

Another very well-crystallised globulin of this class is the protein of the Para nut (*Bertholletia excelsa*), which has been called *excelsin* by Osborne. It occurs in a crystalline form in the aleurone grains in the endosperm of this fruit, and can be easily obtained as hexagonal crystals in a similar way to that described for edestin, which it resembles in character and composition. Its hydrolytic cleavage products have recently been isolated by Osborne and Clapp. A striking feature is the unusually large proportion of arginine found (16 per cent.). A very similar protein has been obtained by Osborne in a crystallised form from oats, and called by him *avenalin.*

The proteins of leguminous plants have been fairly well examined, and must be included in this class. The globulin of beans, which is called *phaseolin* (discovered by Ritthausen), amounts to about 20 per cent. of the seeds, which contain also about 2 per cent. of a second globulin of a greater solubility called *phaselin.* They contain less nitrogen and sulphur than edestin and excelsin. The globulin of peas is called *legumin.* It is not precipitated by sodium chloride or magnesium sulphate on saturation, and gives a rose-red biuret reaction, like peptone. It is also only partially coagulated by heat. The mono-amino-acids of its hydrolytic products have been examined by Abderhalden and Babkin, and these are very similar to those obtained from *conglutin*, the protein isolated by Ritthausen (and subsequently studied by Osborne) from lupins. The name of conglutin had formerly been given to a series of proteins isolated from almonds, peach kernels, walnuts, etc. Osborne and Campbell showed that these proteins differed from conglutin, and accepted the name "amandin" originally given by Proust, for the protein of almonds and peaches. The protein of the hazel nut (*Corylus*) has been called *corylin* by Osborne and Harris. This differs from the globulin of walnuts (*Juglans*), which has been termed *juglansin* by the same observers, in containing more amide-nitrogen, and in being less readily precipitable by ammonium sulphate. For the separation and

distinction of these and other vegetable proteins, fractional precipitation by ammonium sulphate (introduced by Hofmeister) and the application of Hausmann's method proved most useful.

3. *The Alcohol-soluble Proteins.*—The substances belonging to this class, for which the general name *gliadin* is proposed, and which possess no direct analogues amongst the animal proteins,[1] are characterised by their unusual property of being easily soluble in dilute alcohol, some even being soluble in 96 per cent. alcohol. Ritthausen was the first to point out that the seeds of wheat, rye, barley, maize, and oats contain proteins which are insoluble in water and salt solution, but readily soluble in alcohol. In wheat these substances, together with the insoluble phyto-casein (glutenin), form the so-called gluten, the adhesive glue-like material, which is of the greatest importance in bread-making, by giving the necessary tenacity to dough. The chemical characteristics of this class are the high amount of glutaminic acid and the absence of glycine and lysine in their cleavage products. Only three substances of this class have so far been studied to any degree. They are called *wheat gliadin*, *zein* (from maize), and *hordein* (from barley).

Wheat Gliadin.—Ritthausen originally distinguished three alcohol-soluble substances in wheat which he called gliadin (plant glue), glutenfibrin, and mucedin. He was, however, unable to separate them quantitatively, and subsequent investigators, especially Osborne and Campbell, returned to the old view of Taddei's that there is only one alcohol-soluble substance, for which they retained the name of *gliadin*. It seems, however, preferable to call it wheat gliadin in distinction from the group name. It is identical with the substance obtained from rye, and amounts to 4 to 5 per cent. of the grain. It is insoluble in absolute alcohol, but easily soluble in 70 to 80 per cent. alcohol, and is precipitated from these solutions by the addition of water. It is especially characterised by the high percentage of glutaminic acid, which it furnishes on hydrolysis, amounting to 36 to 37 per cent., and the total absence of lysine among its cleavage products. On account of the strikingly different percentages of cleavage products from those of animal proteins, it was chosen by Abderhalden

[1] Pick suggests a similarity to the proto-albumoses.

and Samuely for an interesting experiment with regard to the synthesis of proteins in the animal body. These observers found that on administering it to a horse which had previously lost a large amount of blood, the composition of the serum proteins remained constant.

The alcohol-soluble protein of maize was called *zein* by Gorham, and subsequently maize-fibrin by Ritthausen. Osborne and Chittenden reinvestigated this substance and retained the name zein. It is characterised by its solubility in even strong alcohol of 96 per cent., and its complete insolubility in water. Glutaminic acid is also present in large quantities among its cleavage products, and lysine is absent. The indole-molecule (tryptophane) is also missing, and zein represents, therefore, a convenient material to investigate the question how far the absence of certain cleavage products influences the nutritive value of a protein. Hopkins and Willcock found that growth was very favourably influenced in young animals by zein and tryptophane, whilst zein itself was insufficient.

Hordein is the name given by Osborne to the alcohol-soluble protein of barley. Its differs somewhat from wheat gliadin in its solubilities, and contains more carbon and less sulphur than the latter. The hydrolytic cleavage products, examined by Osborne and Clapp, resemble quantitatively those of the other gliadins. Lysine is absent, and as much as 41 per cent. glutaminic acid was found. The most marked feature, however, is presented by the very large percentage of proline (pyrrolidine-carboxylic acid), which exceeds that yet obtained from any other protein, being practically 14 per cent., or twice as much as that yielded by wheat gliadin.

4. *The Phyto-caseins (or Phyto-vitellins).*—These substances are found in maize, barley, rye, and wheat, and amount in some cases to nearly 50 per cent. of the total protein. When these seeds are completely extracted by treatment with water, followed by salt solution and subsequently alcohol, the residue still contains a large amount of protein, which can only be extracted by treatment with very dilute (0·2 per cent.) alkali. From this solution they are precipitated by neutralisation with acids. They are insoluble in water and alcohol, but show both acid and basic properties, being easily soluble in a slight excess of alkali or acid. The question of their per-

centage of phosphorus has not yet been definitely settled. It may be mentioned here that, according to the unpublished results of an investigation carried out by Dr. Kajiura and the author on the proteins of rice, this cereal also contains a similar substance, which forms the bulk of the rice proteins. Curiously enough, although rice forms the staple food of Oriental races, its proteins have not until now been examined.

The best-known representative of this class is *glutenin*, the alcohol-insoluble part of gluten of wheat. This substance may be easily prepared by the method explained above. In distinction from its constant companion, the wheat gliadin, it furnishes only 9 per cent. glutaminic acid, and contains 2 per cent. lysine amongst its cleavage products. The main interest consists in its connection with gluten-formation. There is still some uncertainty about the process of gluten-formation and the conditions regulating it. The question is an important economic one, as it is intimately connected with the "strength" of flour—*i.e.* the property of wheat which makes it pre-eminently suitable for bread-making.[1] The stiff coherent mass which is formed when wheat-flour is mixed with cold water owes its formation to the presence of proteins, for no such action takes place when pure wheat-starch is mixed with cold water. The question arises whether the gluten proteins exist pre-formed in the grain, or whether they are produced by a secondary change. Weyl and Bischoff compared this process to fibrin formation from fibrinogen in the coagulation of blood, and they assumed the existence of a ferment which transforms in the presence of water the gluten-forming substances into gluten. They were, however, unable to demonstrate such a ferment, and the experiments of Osborne and Voorhees, although they do not exclude ferment action altogether, seem to prove that gluten is formed by the chemical or physical interaction of its two constituents—the gliadin and glutenin. Attempts have been made to explain the relative "strength" of flour from wheat and other cereals by the quantitative relationship of glutenin to gliadin. It seems, however, to be more likely to depend on the physical state of the gluten, which is, as already shown by Ritthausen and Osborne, dependent on the presence of mineral salts.

[1] See A. E. Humphries, SCIENCE PROGRESS, vol. ii. 1907, 175.

It might be mentioned finally that, amongst the vegetable proteins, albumose-like substances have also been met with, but their existence as such in seeds is doubtful. Small quantities of peptones have also been observed.

Typical nucleo-proteins occur in plants. The nucleic acid, isolated by Kossel from yeast, was the first substance of this type known. Osborne and Harris have lately isolated and investigated very thoroughly a nucleic acid from wheat embryos. It furnishes characteristic purine bases on hydrolysis.

(To be continued)

REVIEWS

Textbooks of Physical Chemistry: Stoichiometry. By SYDNEY YOUNG, D.Sc., F.R.S. Also an "Introduction to the Study of Physical Chemistry," by Sir William Ramsay, K.C.B., F.R.S., Editor of the Series. [Pp. lxi. + 381.] London: Longmans, Green & Co. *7s. 6d.*

NEARLY four years have elapsed since the first of these textbooks was issued. In that first volume the hope was expressed that the others of the series would be ready for the press before the end of 1904. This hope has not been realised; but so long as slight delay secures excellence of workmanship, and so long as the contents of each volume are brought up to date, one is prepared to cease grumbling and give a hearty welcome to each belated arrival.

In the case of two of the previous volumes there was just ground for complaint of the excessive bulk and price; treatises on Spectroscopy and Stereochemistry extending to 500 or 600 pages are really quite beyond the limits of a textbook, and out of proportion to the scale of the earlier volumes of the series.

It is therefore gratifying to find that Professor Young, notwithstanding the fundamental and extensive character of his subject, has contrived to give an excellent presentation of it within a reasonable compass. In gauging the extent of the ground which he has to cover, it must be remembered that "stoichiometry" means a good deal more nowadays than it once did. Although not a very common word, it is more than a century since it was first used by Richter to denote the determination of the proportions in which substances combine. Subsequently the meaning has been extended to comprehend not only the determination of atomic and molecular weights, but also the study of the general properties of gases, liquids, and solids, the behaviour of mixtures, solubility, the properties of dilute solutions, and other kindred subjects.

On the relationship between the gaseous and the liquid states, and on cognate problems, Professor Young is especially qualified to write, in virtue of his own extensive and admirable investigations, but in the other parts of the book also the treatment is generally good. A critical perusal of the two chapters on the determination of atomic weights may be recommended, for much loose thinking on this subject is current even among advanced students.

As regards the division of the available space among the various sections of stoichiometry, and as regards the arrangement of the chapters, there is some room for criticism. Only twenty-four pages are allotted to the consideration of the properties of dilute solutions—a space which, in view of the part played by dilute solutions in the development of modern physical chemistry, is decidedly inadequate. When this small space is compared with the 130 pages devoted in a previous volume to the subject of steric hindrance it is obvious that the scale of treatment by the different authors of the textbooks has been very far from uniform.

The chapter on the properties of dilute solutions not only suffers from undue brevity; in one respect, at least, it has not been brought up to date. The last

few years have witnessed a remarkable advance in our experimental knowledge of osmotic pressure—an advance chiefly due to Lord Berkeley and Mr. Hartley, on the one hand, and to Messrs. Morse and Frazer, on the other. The work of the latter investigators is of the utmost importance, involving an extension to concentrated solutions of van 't Hoff's formula for dilute solutions. In Professor Young's discussion of osmotic pressure, however, no reference is made to Morse and Frazer's work.

In regard also to the arrangement of the chapters a word of criticism may be permitted. To devise an arrangement which should be universally acceptable is perhaps a vain hope, but it does seem curious that a chapter on "The Dissociation of Gases and Vapours" should be placed between one on "The Periodic Law" and one on "The Properties of Liquids." The author may have a good reason for this arrangement, but it would seem more rational to discuss cases of abnormal vapour density in that portion of the book which deals with the molecular weights of gases and vapours. Again, the insertion of a discussion of the kinetic gas theory between chapters on the properties of liquids and the properties of solids is open to criticism. It is no doubt true that this theory is closely connected with van der Waals' equation of state, but it should be discussed primarily in relation to the experimental gaseous laws. The three gaseous laws which must be regarded as fundamental by the physical chemist are (1) Boyle's Law, (2) Gay Lussac's Law, (3) Gay Lussac's Law of Volumes, and the descriptive exposition of these should be followed immediately by a discussion of their theoretical basis in the kinetic gas theory and Avogadro's hypothesis.

But although there thus appears to be some ground for criticism, Professor Young's volume may be cordially commended to all those who seek to familiarise themselves with the point of view of physical chemistry—a point of view which is both rational and stimulating.

J. C. PHILIP.

Physiography. By ROLLIN D. SALISBURY, Professor of Geology and Head of the Department of Geography in the University of Chicago. London: John Murray. 1907.

IN this country the term physiography is applied by the Board of Education to an assemblage of theoretical and experimental material, gathered from nearly every branch of science, to form a subject for instruction and examination in our elementary schools. In the United States, on the other hand, it is employed with a more definite meaning and concerns itself with the physical aspects of our planet and their variations in time and space. It is a favourite study in the higher classes in schools, and lower classes in colleges, and the present volume is one of the best that has appeared in recent years to satisfy the demand for a text-book on the subject. Its most striking characteristic is its wealth in illustration. Every stage in the evolution of the land is depicted in clearly reproduced photographs of American scenery; the diagrams are striking, and in many cases original; but a still more important feature is the number of maps. These include effective photographs from models, graphic representations of the distribution of physical phenomena, and transcripts and facsimiles of the topographical maps of the United States Geological Survey. These last are closely contoured, and give an excellent idea of the form of the earth's surface. One is glad to be reminded by the author that the originals can be obtained from the Director of the Survey at Washington at the rate of three dollars a hundred, which works

out at about three-halfpence each. The author is to be congratulated on the fact that he has in every case restricted his maps and diagrams within the limits of the format of the book, thus avoiding the inconvenience of folded sheets.

Though showing occasional traces of haste, the text is as a rule clear and readable, besides containing much that is suggestive and original. Perhaps the least satisfactory portion of the book is that which deals with the regional distribution of pressure in high latitudes, the explanations that are offered being hardly calculated to carry conviction to the mind of the student. It is true that much remains to be done in working out the details of the subject ; but the main principles admit of very simple expression. Briefly, the variations in pressure on the earth's surface are dependent on differences of temperature, moisture, and centrifugal force—to use a useful term by no means free from objection but sufficiently well understood. The tendency of heat alone would be to make the pressure increase continuously from the equator to the poles. That of centrifugal force alone has exactly the contrary effect, for air moving towards the poles has a greater rotational velocity than that proper to its new latitude, and therefore tends to rise, while air moving towards the equator tends to sink. The magnitude of this effect is dependent on the rate of change in the length of the radius of rotation, a rate which increases rapidly as the pole is approached. Thus it comes about that while the influence of heat difference is greater in low latitudes that of difference of centrifugal force is more powerful in high latitudes. If then the earth were a uniform solid spheroid, there would be a belt of low pressure round the equator and two areas of low pressure at the poles with high-pressure belts between. In the colder regions, however, the air over the open sea is as a rule warmer as well as moister than that over ice or land masses. Tracts of open sea in high latitudes are therefore characterised by abnormally low pressure. Accordingly we find in the North Atlantic and Pacific two areas of low pressure imposed upon the regular decrease of pressure from the horse latitudes to the North Pole itself. Similarly in the Southern Hemisphere the open circum-antarctic sea gives rise to a circle of abnormally low pressure. Beyond, in the region of Antarctic land and ice, the pressure is probably somewhat higher, representing the normal low pressure of the pole.

There are some minor points on which a word of explanation might have been added for the benefit of English readers. For instance, on page 509 we find the word "billion" used in the popular American sense of a thousand million instead of the square of a million, according to the usage of mathematicians, though, curiously enough, in a quotation from Sir John Herschell, on the very next page, a trillion is employed correctly, without comment, for the cube of a million. On page 613 we are told that the "English" unit of pressure gradient is a hundredth of an inch in seventeen miles, which appears a very unreasonable convention in the absence of the explanation that it is equivalent to one millimetre in a degree.

These however are minor matters. The book as a whole is excellent, and the best testimony to its value is the keen interest it has awakened in every student in whose hands it has been placed.

JOHN W. EVANS.

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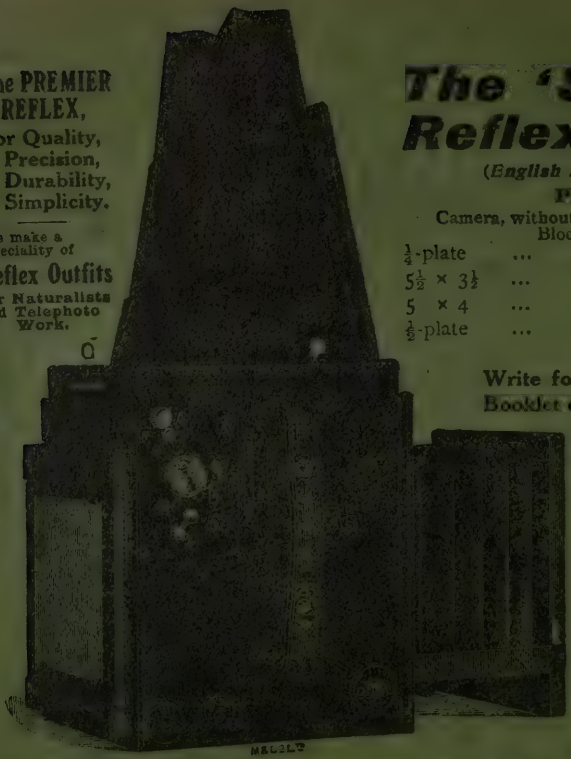

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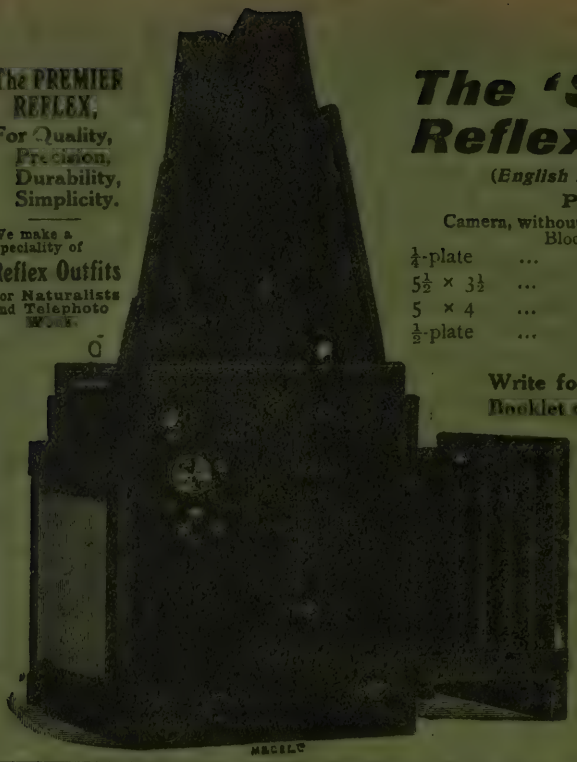

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